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 NEWS  2           "Ask CAS" for self-help around the clock
 NEWS  3  SEP 09   ACD predicted properties enhanced in REGISTRY/ZREGISTRY
 NEWS  4  OCT 03   MATHDI removed from STN
 NEWS  5  OCT 04   CA/CAplus-Canadian Intellectual Property Office (CIPO) added
                   to core patent offices
 NEWS  6  OCT 13   New CAS Information Use Policies Effective October 17, 2005
 NEWS  7  OCT 17   STN(R) AnaVist(TM), Version 1.01, allows the export/download
                   of CAplus documents for use in third-party analysis and
                   visualization tools
 NEWS  8  OCT 27   Free KWIC format extended in full-text databases
 NEWS  9  OCT 27   DIOGENES content streamlined
 NEWS 10  OCT 27   EPFULL enhanced with additional content
 NEWS 11  NOV 14   CA/CAplus - Expanded coverage of German academic research

 NEWS EXPRESS  NOVEMBER 18 CURRENT VERSION FOR WINDOWS IS V8.01,
               CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 13 JUNE 2005.
               V8.0 USERS CAN OBTAIN THE UPGRADE TO V8.01 AT
               http://download.cas.org/express/v8.0-Discover/

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FILE 'HOME' ENTERED AT 17:43:34 ON 25 NOV 2005

=> file caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

FILE 'CAPLUS' ENTERED AT 17:43:43 ON 25 NOV 2005
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FILE COVERS 1907 - 25 Nov 2005 VOL 143 ISS 23
FILE LAST UPDATED: 24 Nov 2005 (20051124/ED)

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They are available for your review at:

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=> s us 2004-0171695/pn
L1 1 US 2004-0171695/PN
(US2004171695/PN)

=> sel rn
E1 THROUGH E4 ASSIGNED

=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	2.42	2.63

FILE 'REGISTRY' ENTERED AT 17:44:19 ON 25 NOV 2005

Property values tagged with IC are from the ZIC/VINITI data file
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STRUCTURE FILE UPDATES: 24 NOV 2005 HIGHEST RN 868731-40-2
DICTIONARY FILE UPDATES: 24 NOV 2005 HIGHEST RN 868731-40-2

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conducting SmartSELECT searches.

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* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *
****

Structure search iteration limits have been increased. See HELP SLIMITS
for details.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document. For information

on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

```
=> s e1-e4
             1 164301-51-3/BI
               (164301-51-3/RN)
             1 165245-96-5/BI
               (165245-96-5/RN)
             1 208197-81-3/BI
               (208197-81-3/RN)
             1 208197-82-4/BI
               (208197-82-4/RN)
L2           4 (164301-51-3/BI OR 165245-96-5/BI OR 208197-81-3/BI OR 208197-82
               -4/BI)

=> d 1-4

L2   ANSWER 1 OF 4  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   208197-82-4  REGISTRY
ED   Entered STN:  09 Jul 1998
CN   DNA, d(P-thio)(G-T-C-T-T-G-T-T-C-A-G-C-T-C-C-T-G-C) (9CI)  (CA INDEX NAME)
FS   NUCLEIC ACID SEQUENCE
MF   Unspecified
CI   MAN
SR   CA
LC   STN Files:   CA, CAPLUS, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
               1 REFERENCES IN FILE CA (1907 TO DATE)
               1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L2   ANSWER 2 OF 4  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   208197-81-3  REGISTRY
ED   Entered STN:  09 Jul 1998
CN   DNA, d(P-thio)(G-C-A-G-G-A-G-C-T-G-A-A-C-A-A-G-A-C) (9CI)  (CA INDEX NAME)
FS   NUCLEIC ACID SEQUENCE
MF   Unspecified
CI   MAN
SR   CA
LC   STN Files:   CA, CAPLUS, USPATFULL

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
               1 REFERENCES IN FILE CA (1907 TO DATE)
               1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L2   ANSWER 3 OF 4  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   165245-96-5  REGISTRY
ED   Entered STN:  26 Jul 1995
CN   Kinase (phosphorylating), protein, RK (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   CSBP
CN   CSBP kinase
CN   CSBP/p38 kinase
CN   Cytokine synthesis anti-inflammatory drug-binding protein
CN   High-osmolarity glycerol response kinase
CN   Hog1 MAP kinase
CN   MAP kinase Hog1p
CN   Mitogen-activated protein kinase 14
CN   Mitogen-activated protein kinase Mxi2
CN   P38 kinase
```

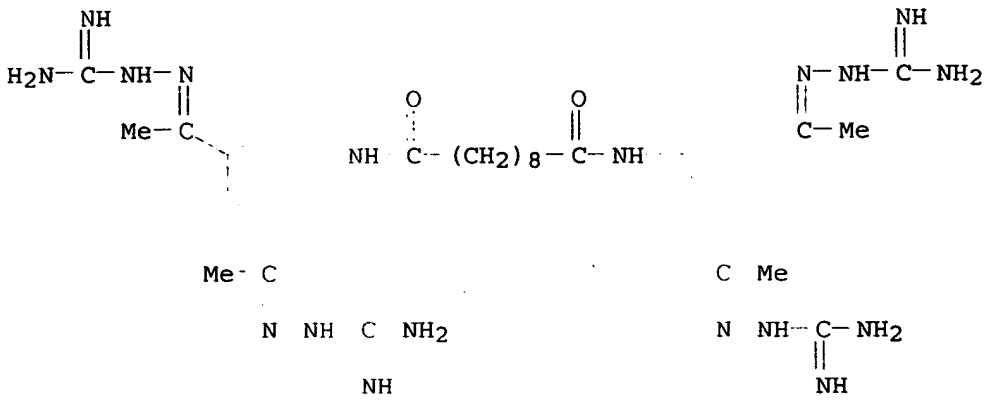
CN p38 MAP kinase
CN p38 MAPK
CN p38 Mitogen-activated kinase
CN p38 Mitogen-activated protein kinase
CN P38-2 mitogen-activated protein kinase
CN p38α MAP kinase
CN p38α Mitogen-activated protein kinase
CN p38/RK
CN Protein kinase HOG1
CN Protein kinase p38/HOG
CN Protein kinase p38/HOG1
CN Protein kinase p38mapk
CN Protein kinase p38SAPK2
CN Protein kinase RK
CN Protein kinase SAPK2a
CN Protein p38α kinase
CN Reactivating kinase
CN SAPK2a/p38 kinase
CN Stress-activated protein kinase p38α
CN Stress-activated protein kinase-2a
CN Stress-activated-protein kinase-2
DR 185402-48-6, 185464-66-8
MF Unspecified
CI MAN
SR CA
LC STN Files: ADISNEWS, AGRICOLA, BIOBUSINESS, BIOSIS, CA, CAPLUS, CASREACT, CEN, CIN, PROMT, TOXCENTER, USPAT2, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

8151 REFERENCES IN FILE CA (1907 TO DATE)
153 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
8195 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L2 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2005 ACS on STN
RN **164301-51-3** REGISTRY
ED Entered STN: 30 Jun 1995
CN Decanediamide, N,N'-bis[3,5-bis[1-[(aminoiminomethyl)hydrazono]ethyl]phenyl]-, tetrahydrochloride (9CI) (CA INDEX NAME)
OTHER NAMES:
CN AXD 455
CN CNI 1493
CN Semapimod tetrahydrochloride
MF C34 H52 N18 O2 . 4 Cl H
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CA, CAPLUS, CIN, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, PROMT, PROUSDDR, SYNTHLINE, TOXCENTER, USPATFULL
CRN (352513-83-8)



● 4 HCl

59 REFERENCES IN FILE CA (1907 TO DATE)
59 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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=> file caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     8.65      11.28

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FILE COVERS 1907 - 25 Nov 2005  VOL 143 ISS 23
FILE LAST UPDATED: 24 Nov 2005  (20051124/ED)

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=> s l2
L3          8242 L2

=> s l3 and p38
           11143 P38
L4          7938 L3 AND P38

=> s l4 and HIV
           63471 HIV
L5            82 L4 AND HIV
```

```
=> s l3 (L) p38
         11143 P38
L6        7775 L3 (L) P38

=> s l6 (L) HiV
         63471 HIV
L7          38 L6 (L) HIV

=> s l7 (L) (MAPK or "map kinase")
         13262 MAPK
         87554 "MAP"
        252214 "KINASE"
         16089 "MAP KINASE"
                 ("MAP"(W)"KINASE")
L8          28 L7 (L) (MAPK OR "MAP KINASE")

=> d 20-28 bib abs hitstr

L8   ANSWER 20 OF 28  CAPLUS  COPYRIGHT 2005 ACS on STN
AN   2000:910634  CAPLUS
DN   134:176557
TI   HIV gp120 enhances NO production by cardiac myocytes through p38 MAP
     kinase-mediated NF-κB activation
AU   Kan, Hong; Xie, Zirong; Finkel, Mitchell S.
CS   Department of Medicine Robert C. Byrd Health Sciences Center, West
     Virginia University School of Medicine, Morgantown, WV, 26506-9157, USA
SO   American Journal of Physiology (2000), 279(6, Pt. 2), H3138-H3143
     CODEN: AJPHAP; ISSN: 0002-9513
PB   American Physiological Society
DT   Journal
LA   English
AB   Human immunodeficiency virus (HIV) infection is associated with a
     surprisingly high frequency of myocardial dysfunction.  Potential
     mechanisms include direct effects of HIV, indirect effects mediated by
     cytokines, or a combination.  We have previously reported that
     interleukin-1β (IL-1β) (500 U/mL) alone induced nitric oxide
     (NO) production by neonatal rat cardiac myocytes (CM).  Effects of the HIV-1
     envelope, glycoprotein120 (gp120), on inducible NO synthase (iNOS) in CM
     have not been previously reported.  Unlike IL-1β, recombinant
     HIV-gp120 (1 μg/mL) alone failed to enhance NO production in CM (0.5±0.4
     vs. 0.4±0.5 μmol/1.25+105 cells/48 h, gp120 vs. control,
     resp.).  However, the addition of gp120 to IL-1β significantly enhanced
     iNOS mRNA expression (70±1.5 vs. 26±2.4 optical units, IL-1β +
     gp120 vs. IL-1β, resp.), iNOS protein synthesis (42±1.4 vs.
     18±0.8 optical units, IL-1β + gp120 vs. IL-1β, resp.), and NO
     production (NO2-) (6.6±0.6 vs. 4.1±0.8 μmol/1.25+105 cells/48
     h, IL-1β + gp120 vs. IL-1β, resp.).  HIV-gp120 enhancement of
     IL-1β-induced NO2- production was blocked by 10 μM of SB-203580 (SB),
     a selective p38 protein kinase inhibitor (3.6±0.2 vs. 6.6±0.6
     μmol/1.25+105 cells/48 h, IL-1β + gp120 + SB vs. IL-1β
     + gp120, resp.).  HIV-gp120-enhanced p38 protein kinase activity was
     associated with an increase in IL-1β-stimulated NF-κB activity
     (184±12.7 vs. 92±10.7 optical units, IL-1β + gp120 vs.
     IL-1β, resp.).  None of these effects was seen with another
     recombinant HIV-1 protein, Tat.  Thus HIV-gp120 enhancement of
     IL-1β-induced NO production is associated with p38-mediated activation of
     NF-κB.  Direct effects of HIV-gp120 on CM may provide a previously
     unrecognized mechanism contributing to HIV cardiomyopathy.
IT   165245-96-5, p38 MAP kinase
     RL: BAC (Biological activity or effector, except adverse); BPR (Biological
     process); BSU (Biological study, unclassified); BIOL (Biological study);
     PROC (Process)
        (HIV gp120 enhances NO production by cardiac myocytes through
        p38 MAP kinase-mediated NF-κB
        activation)
```

RN 165245-96-5 CAPLUS
CN Kinase (phosphorylating), protein, RK (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 21 OF 28 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:68907 CAPLUS
DN 132:232667
TI Activation of NF-κB and p38 MAP Kinase Is Not Sufficient for Triggering Efficient HIV Gene Expression in Response to Stress
AU Taher, Mohiuddin M.; Oakley, Jacqueline D.; Hershey, Chad; Valerie, Kristoffer
CS Department of Radiation Oncology and Massey Cancer Center Medical College of Virginia, Virginia Commonwealth University, Richmond, VA, 23298-0058, USA
SO Biochemistry (2000), 39(7), 1709-1715
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English
AB Recent studies have established an essential role for p38 MAP kinase in UV activation of human immunodeficiency virus (HIV) gene expression. However, p38 MAP kinase is not involved in activation of NF-κB, a key transcriptional activator of HIV gene expression, in response to UV, suggesting that NF-κB acts independently of p38 MAP kinase. In this study, we have investigated whether activation of HIV gene expression occurs when p38 MAP kinase and NF-κB are activated by sep. stress-causing treatments, each relatively specific for activating only one of the factors. Treatment of cells with sorbitol (hyperosmotic shock) strongly activates p38 MAP kinase, whereas the cytokine TNF-α is a poor activator of p38 MAP kinase. On the other hand, TNF-α is a strong activator of NF-κB whereas sorbitol is not. Sorbitol, however, activates AP-1 DNA binding activity in a manner similar to that of UV. Most importantly, both sorbitol and TNF-α are poor activators of HIV gene expression in HeLa cells stably transfected with an HIVcat reporter gene, whereas UV elicits a strong response. The combined treatment with UV and hyperosmotic shock produces an additive effect on HIV gene expression, suggesting that these agents activate at least in part by different mechanisms. The combined treatment with sorbitol and TNF-α activates p38 and NF-κB to levels similar to those with UV, yet only results in 25-30% of the CAT levels elicited by UV. Inhibition of NF-κB activation by the protease inhibitor N-α-tosyl-L-phenylalanine chloromethyl ketone (TPCK) prevents UV activation of HIV gene expression, but does not inhibit p38 MAP kinase activation. We conclude that whereas both p38 MAP kinase and NF-κB are important for UV activation of HIV gene expression they act independently from each other and activation of both factors is not sufficient for triggering a full HIV gene expression response. Activation of HIV gene expression by UV must therefore involve addnl. cellular processes, such as those triggered by DNA damage, for generation of a full gene expression response.
IT **165245-96-5, p38 MAP kinase**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(activation of NF-κB and **p38 MAP kinase** is not sufficient for triggering efficient **HIV** gene expression in response to stress)
RN 165245-96-5 CAPLUS
CN Kinase (phosphorylating), protein, RK (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RE.CNT 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 22 OF 28 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:580102 CAPLUS
DN 131:297126
TI Genetic Evidence That Stress-Activated p38 MAP Kinase Is Necessary but Not Sufficient for UV Activation of HIV Gene Expression
AU Taher, Mohiuddin M.; Baumgardner, Timothy; Dent, Paul; Valerie, Kristoffer
CS Department of Radiation Oncology and Massey Cancer Center Medical College of Virginia, Virginia Commonwealth University, Richmond, VA, 23298-0058, USA
SO Biochemistry (1999), 38(40), 13055-13062
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English
AB We have examined the role of stress-activated p38 MAP kinase in regulating human immunodeficiency virus (HIV) gene expression in response to UV light (UV). We found that UV activated p38 in HeLa cells harboring stably integrated copies of an HIVcat plasmid to levels similar to those obtained by hyperosmotic shock. However, hyperosmotic shock resulted in one order of magnitude smaller increase in CAT activity than treatment with UV. The specific p38 inhibitor SB203580 significantly decreased (>80%) UV activation of HIV gene expression whereas PD98059, a specific MEK-1 inhibitor did not, suggesting that p38 is specifically involved in the HIV UV response and little to no contribution is provided by MEK-1 and the p42/p44 MAP kinase pathway. Whereas increased binding of NF-κB to an oligonucleotide spanning the HIV enhancer was observed after UV, as expected, this binding was not affected by SB203580. Furthermore, UV activation of HIV gene expression in cells having the cat reporter gene under control of an HIV promoter deleted of the enhancer (-69/+80) produced results indistinguishable from those using HIVcat/HeLa cells with an intact HIV promoter (-485/+80), suggesting that SB203580 acts through the basal transcription machinery. Northern blot anal. of steady-state RNA from HIVcat/HeLa cells revealed an almost complete inhibition of UV activation with SB203580 at the RNA level. Similarly, the UV response was almost completely obliterated at the CAT and RNA levels in HIVcat/HeLa cells stably transfected with a plasmid expressing a kinase-inactive mutant of p38 (isoform α), without affecting NF-κB activation, providing strong genetic evidence that p38, at least the α isoform, is necessary for UV activation of HIV gene expression and that NF-κB activation alone is insufficient. These results firmly establish p38 MAP kinase as a key modulator of HIV gene expression in response to UV that acts independently of NF-κB.
IT **165245-96-5, p38 MAP kinase**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(stress-activated **p38 MAP kinase**: necessary but not sufficient for UV activation of **HIV** gene expression)
RN 165245-96-5 CAPLUS
CN Kinase (phosphorylating), protein, RK (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 23 OF 28 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:507831 CAPLUS
DN 131:256239
TI Chemokines and activated macrophages in HIV gp120-induced neuronal apoptosis
AU Kaul, Marcus; Lipton, Stuart A.
CS CNS Research Institute, Brigham and Women's Hospital, and Program in Neuroscience, Harvard Medical School, Boston, MA, 02115, USA

SO Proceedings of the National Academy of Sciences of the United States of America (1999), 96(14), 8212-8216
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
AB HIV-1 glycoprotein gp120 induces injury and apoptosis in rodent and human neurons in vitro and in vivo and is therefore thought to contribute to HIV-associated dementia. In addition to CD4, different gp120 isolates bind to the α- or β-chemokine receptors CXCR4 and CCR5, resp. These and other chemokine receptors are on brain macrophages/microglia, astrocytes, and neurons. Thus, apoptosis could occur via direct interaction of gp120 with neurons, indirectly via stimulation of glia to release neurotoxic factors, or via both pathways. Here we show in rat cerebrocortical cultures that recapitulate the type and proportion of cells normally found in brain, i.e., neurons, astrocytes, and macrophages/microglia, that the β-chemokines RANTES (regulated on activation, normal T cell expressed and secreted) and macrophage inflammatory protein (MIP-1β) protect neurons from gp120SF2-induced apoptosis. The gp120SF2 isolate prefers binding to CXCR4 receptors, similar to the physiol. α-chemokine ligands, stromal cell-derived factor (SDF)-1α/β. SDF-1α/β failed to prevent gp120SF2 neurotoxicity, and in fact also induced neuronal apoptosis. We could completely abrogate gp120SF2-induced neuronal apoptosis with the tripeptide TKP, which inhibits activation of macrophages/microglia. In contrast, TKP or depletion of macrophages/microglia did not prevent SDF-1 neurotoxicity. Inhibition of p38 mitogen-activated protein kinase ameliorated both gp120SF2- and SDF-1-induced neuronal apoptosis. Taken together, these results suggest that gp120SF2 and SDF-1 differ in the cell type on which they stimulate CXCR4 to induce neuronal apoptosis, but both ligands use the p38 mitogen-activated protein kinase pathway for death signaling. Moreover, gp120SF2-induced neuronal apoptosis depends predominantly on an indirect pathway via activation of chemokine receptors on macrophages/microglia, whereas SDF-1 may act directly on neurons or astrocytes.
IT **165245-96-5, p38 MAP kinase**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(chemokines and activated macrophages in **HIV** gp120-induced neuronal apoptosis via)
RN 165245-96-5 CAPLUS
CN Kinase (phosphorylating), protein, RK (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 24 OF 28 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:32940 CAPLUS
DN 130:195661
TI Activation-induced resistance of human macrophages to HIV-1 infection in vitro
AU Zybarth, Gabriele; Reiling, Norbert; Schmidtmayerova, Helena; Sherry, Barbara; Bukrinsky, Michael
CS The Picower Institute for Medical Research, Manhasset, NY, 11030, USA
SO Journal of Immunology (1999), 162(1), 400-406
CODEN: JOIMA3; ISSN: 0022-1767
PB American Association of Immunologists
DT Journal
LA English
AB Cells of the monocyte/macrophage lineage are the first targets of HIV-1 in patients and also serve as reservoirs for the virus during the course of infection. The authors investigated the effects of cell activation on early events of HIV-1 infection of monocyte-derived macrophages. Addition of

LPS, a potent stimulator of macrophages, at the time of infection stimulated entry of HIV-1 into monocyte-derived macrophages, as judged by accumulation of early products of RT, but inhibited the synthesis of late RT products and strongly repressed nuclear import of the viral DNA, resulting in protection from infection. This effect was mediated by the CD14 receptor and involved activation of the p38 mitogen-activated protein kinase pathway. Disruption of this signaling pathway using a specific inhibitor of the p38 mitogen-activated protein kinase (SB 203580) restored HIV-1 infection in the presence of LPS. These results suggest a novel view of the role of macrophage activation in anti-HIV responses of the immune system.

IT **165245-96-5, p38 MAP kinase**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(CD14-mediated activation of human macrophages induces **p38** kinase-dependent resistance to **HIV**-1 infection)

RN 165245-96-5 CAPLUS
CN Kinase (phosphorylating), protein, RK (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RE.CNT 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 25 OF 28 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:679946 CAPLUS
DN 130:37222
TI Interleukin 18 stimulates HIV type 1 in monocytic cells
AU Shapiro, Leland; Puren, Adrian J.; Barton, Hazel A.; Novick, Daniela; Peskind, Robert L.; Shenkar, Robert; Gu, Yong; Su, Michael S.-S.; Dinarello, Charles A.
CS Department of Medicine, University of Colorado Health Sciences Center, Denver, CO, 80262, USA
SO Proceedings of the National Academy of Sciences of the United States of America (1998), 95(21), 12550-12555
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
AB The cytokine interleukin (IL) 18 (formerly interferon γ-inducing factor) induces the T helper type 1 response. Here, IL-18 increased HIV type 1 (HIV-1) production from 5- to 30-fold in the chronically infected U1 monocytic cell line. Inhibition of tumor necrosis factor (TNF) activity by the addition of TNF-binding protein reduced IL-18-stimulated HIV-1 production by 48%. In the same cultures, IL-18-induced IL-8 was inhibited by 96%. Also, a neutralizing anti-IL-6 mAb reduced IL-18-induced HIV-1 by 63%. Stimulation of U1 cells with IL-18 resulted in increased production of IL-6, and exogenous IL-6 added to U1 cells increased HIV-1 production 4-fold over control. A specific inhibitor of the p38 mitogen-activated protein kinase reduced IL-18-induced HIV-1 by 73%, and a 50% inhibition was observed at 0.05 μM. In the same cultures, IL-8 was inhibited by 87%. By gel-shift and supershift analyses, increased binding activity of the transcription factor NF-κB was measured in nuclear exts. from U1 cells 1 h after exposure to IL-18. These results demonstrate induction of HIV-1 by IL-18 in a monocyte target associated with an intermediate role for TNF and IL-6, activation of p38 mitogen-activated protein kinase, and nuclear translocation of NF-κB.

IT **165245-96-5, p38 MAP kinase**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(interleukin 18 stimulates **HIV**-1 in monocytes via formation of tumor necrosis factor and interleukin-6, activation of **p38 MAP kinase**, and nuclear translocation of NF-κB)

RN 165245-96-5 CAPLUS
CN Kinase (phosphorylating), protein, RK (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 26 OF 28 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:414266 CAPLUS
DN 129:147915
TI Role of p38 mitogen-activated protein kinase in HIV type 1 production in vitro
AU Shapiro, Leland; Heidenreich, Kim A.; Meintzer, Mary Kay; Dinarello, Charles A.
CS Department of Medicine, Division of Infectious Diseases, University of Colorado Health Sciences Center, Denver, CO, 80262, USA
SO Proceedings of the National Academy of Sciences of the United States of America (1998), 95(13), 7422-7426
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
AB The proinflammatory cytokines interleukin (IL)-1 and tumor necrosis factor (TNF) promote HIV type 1 viral replication in vitro. In the present studies, HIV production was increased in the macrophagic U1 cell line expressing the HIV genome after exposure to IL-1β, osmotic stress, or surface adhesion, suggesting a confluence of signaling pathways for proinflammatory cytokines and cell stressors. The p38 mitogen-activated protein kinase (MAPK) mediates both cytokine and stress responses; thus the role of this kinase in HIV production was investigated. HIV production as measured by p24 antigen correlated with changes in the expression of a specific (non-alpha) isoform of p38 MAPK. In the presence of a specific p38 MAPK inhibitor (p38 inh), IL-1β-induced HIV production was suppressed by more than 90% and IL-1β-induced IL-8 production was suppressed completely, both with IC50 of 0.01 μM. P38 inhibition blocked cell-associated p24 antigen and secreted virus to a similar extent. The p38 inhibitor also decreased constitutive HIV production in freshly infected peripheral blood mononuclear cells by up to 50% ($P < 0.05$). Interruption of p38 MAPK activity represents a viable target for inhibition of HIV.
IT **165245-96-5, p38 MAP kinase**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); MFM (Metabolic formation); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); USES (Uses)
(role of **p38** mitogen-activated protein kinase in **HIV** type 1 production in vitro)
RN 165245-96-5 CAPLUS
CN Kinase (phosphorylating), protein, RK (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RE.CNT 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 27 OF 28 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1997:408565 CAPLUS
DN 127:107891
TI The critical role of p38 MAP kinase in T cell HIV-1 replication
AU Cohen, Pamela S.; Schmidtmayerova, Helena; Dennis, Jameel; Dubrovsky, Larisa; Sherry, Barbara; Wang, Haichao; Bukrinsky, Michael; Tracey, Kevin J.
CS The Picower Institute for Medical Research, Manhasset, NY, 11030, USA
SO Molecular Medicine (New York) (1997), 3(5), 339-346
CODEN: MOMEF3; ISSN: 1076-1551
PB Springer
DT Journal
LA English
AB Replication of HIV-1 in human T lymphocytes requires the activation of host cellular proteins. This study identifies p38 mitogen-activated

protein kinase (MAPK) as one such kinase necessary for HIV-1 replication in T cells. Primary human T lymphocytes were infected with the LAI strain of HIV-1 and Jurkat cells were infected with the RF strain of HIV-1. HIV replication was measured by reverse transcriptase activity. Cellular expression of endogenous p38 MAPK protein was analyzed using immunopptn. Blockade of p38 MAPK expression was achieved using antisense oligonucleotides to p38 MAPK and the guanylhydrazone compound CNI-1493, an inhibitor of p38 MAPK activation. HIV-1 infection of both primary human T lymphocytes and a T cell line rapidly activated the cellular p38 MAPK pathway, which remained activated for the duration of the culture. Addition of phosphothioated antisense oligonucleotides to p38 MAPK specifically inhibited viral replication. Blockade of p38 MAPK activation by addition of CNI-1493 also inhibited HIV-1 viral replication of primary T lymphocytes in a dose- and time-dependent manner. Stimulation of p38 MAPK activation did not occur with the addition of heat-inactivated virus, suggesting that viral internalization, and not just membrane binding, is necessary for p38 MAPK activation. These results indicate that activation of the p38 MAPK cascade is critical for HIV-1 replication in primary T lymphocytes, and that blockade of this signal transduction pathway may be a novel therapeutic approach to the treatment of HIV-1 infection.

IT **165245-96-5, p38 MAP kinase**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**p38 MAP kinase** in **HIV**-1 replication in infected humans T-cells)

RN 165245-96-5 CAPLUS

CN Kinase (phosphorylating), protein, RK (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 28 OF 28 CAPLUS COPYRIGHT 2005 ACS on STN

AN 1996:732804 CAPLUS

DN 126:30209

TI Activation of the HIV-1 long terminal repeat by cytokines and environmental stress requires an active CSBP/p38 MAP kinase

AU Kumar, Sanjay; Orsini, Michael J.; Lee, John C.; McDonnell, Peter C.; Debouck, Christine; Young, Peter R.

CS Dep. Mol. Immunol., SmithKline Beecham Pharmaceuticals, King of Prussia, PA, 19406, USA

SO Journal of Biological Chemistry (1996), 271(48), 30864-30869
CODEN: JBCHA3; ISSN: 0021-9258

PB American Society for Biochemistry and Molecular Biology

DT Journal

LA English

AB The human immunodeficiency virus, type 1 (HIV-1) promoter is known to be activated by proinflammatory cytokines and UV light. These stimuli also activate various members of the mitogen-activated protein kinase family, including JNK/SAPK and CSBP/p38. In HeLa cells containing an integrated HIV-1 long terminal repeat (LTR)-driven reporter, we now show that the specific p38 inhibitor, SB203580, inhibits activation of the HIV-1 LTR by interleukin-1, tumor necrosis factor, UV light, and osmotic stress. Inhibition was 70-90% in all but the case of tumor necrosis factor stimulation, where inhibition was 50%. Each of these stimuli activated p38, which was inhibited by SB203580 in vitro and in vivo with an IC50 (between 0.1 and 1 μM) similar to that required to inhibit transcription. In contrast, SB203580 had no effect on JNK, which was also activated by these stimuli. The NFκB sites in the HIV-1 LTR were required for a response to cytokines but not to UV, and SB203580 remained capable of inhibiting UV activation in the absence of the NFκB sites. Studies in which SB203580 was added at different times relative to UV stimulation suggested that the critical p38-mediated phosphorylation event occurred between 2 and 4 h after UV treatment. These data indicate that p38 is required for HIV-1 LTR activation but that the action of p38 is delayed, presumably due to substrate unavailability or inaccessibility.

IT **165245-96-5, p38 MAP kinase**
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(activation of the **HIV**-1 long terminal repeat by cytokines and environmental stress requires an active CSBP/**p38 MAP kinase**)
RN 165245-96-5 CAPLUS
CN Kinase (phosphorylating), protein, RK (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

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             0 164301-51-3D
L9          59 164301-51-3/RN
                 (164301-51-3 (NOTL) 164301-51-3D )

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         13262 "MAPK"
         87554 "MAP"
        252214 "KINASE"
         16089 "MAP KINASE"
                 ("MAP"(W)"KINASE")
L10      95386 L9 (L) P38 OR ("MAP" OR "MAPK" OR "MAP KINASE")

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          13262 "MAPK"
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          16089 "MAP KINASE"
                  ("MAP"(W)"KINASE")
L11           6 L9 (L) (P38 OR ("MAP" OR "MAPK" OR "MAP KINASE"))

=> d 1-6 bib abs hitstr

L11  ANSWER 1 OF 6  CAPLUS  COPYRIGHT 2005 ACS on STN
AN   2005:1004352  CAPLUS
DN   143:279459
TI   Compositions and methods for preventing and treating skin and hair
     conditions
IN   David, Nathaniel E.
PA   VVII NewCo 2003, Inc., USA
SO   U.S. Pat. Appl. Publ., 16 pp.
     CODEN: USXXCO
DT   Patent
LA   English
FAN.CNT 3
     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
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PI   US 2005203111         A1    20050915    US 2004-799867          20040312
     WO 2005091891         A2    20051006    WO 2005-US6300          20050225
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM,
             SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
             EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,
             RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
             MR, NE, SN, TD, TG
PRAI US 2004-799540       A     20040311
     US 2004-799867       A     20040312
     US 2004-810391       A     20040326
AB   The present invention discloses compns. and methods for the prevention and
     treatment of skin and hair diseases, such as, for example, alopecia,
     psoriasis, and keloids.  In one embodiment, the present invention
     discloses a method for preventing and treating hair loss by applying
     locally to a region lacking hair a p38α MAP kinase inhibitor.  The
     p38α MAP kinase inhibitor is preferably formulated as a gel,
     ointment, spray or solution that can be applied topically, transdermally, or
     s.c. to the targeted region.  The p38 inhibitor is especially RDP-58, AMG-548,
     BIRB-796, CNI-1493, VX-702 or VX-745.
IT   164301-51-3, CNI-1493
     RL: BSU (Biological study, unclassified); PAC (Pharmacological activity);
     THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (as inhibitor; p38.alpha. MAP kinase
        inhibitor for preventing and treating skin and hair conditions)
RN   164301-51-3  CAPLUS
CN   Decanediamide, N,N'-bis[3,5-bis[1-[(aminoiminomethyl)hydrazono]ethyl]pheny
     l]-, tetrahydrochloride (9CI)  (CA INDEX NAME)
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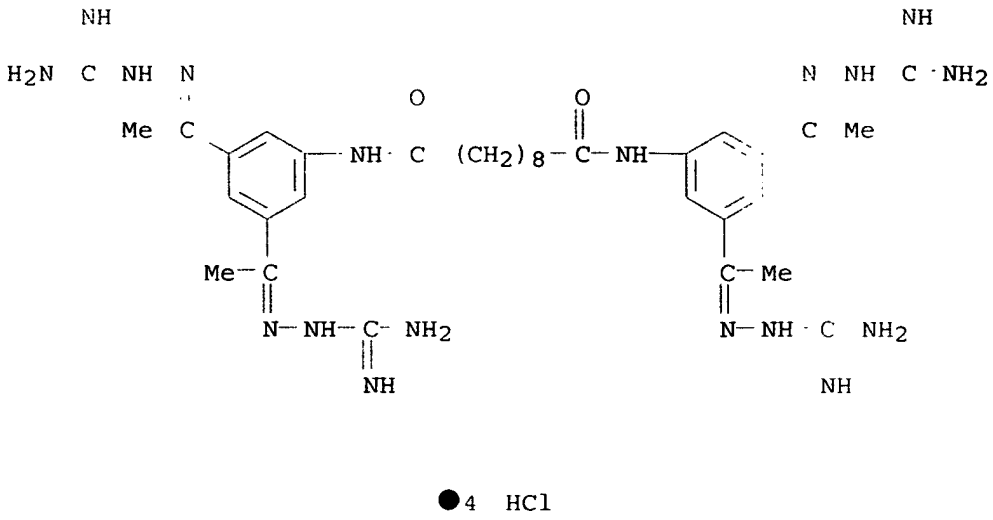

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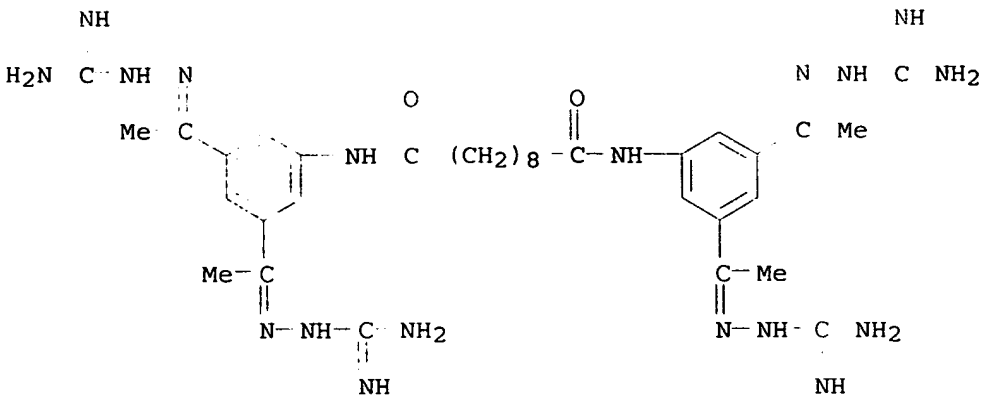
L11 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:698408 CAPLUS
DN 140:285883
TI Differential p38 mitogen-activated protein kinase target phosphorylation in responders and nonresponders to infliximab. Response to comments on pp. 633-634
AU Peppelenbosch, Maikel P.; Van Den Blink, Bernt; Van Deventer, Sander J. H.; Hommes, Daniel
CS Department of Gastroenterology and Hepatology, Academic Medical Center, University of Amsterdam, Amsterdam, Neth.
SO Gastroenterology (2003), 125(2), 635-636
CODEN: GASTAB; ISSN: 0016-5085
PB W. B. Saunders Co.
DT Journal
LA English
AB A polemic in response to Schreiber et al. (ibid 633-634). Schreiber cum suis observed the difference in infliximab-induced phosphorylation of the proinflammatory transcription factor ATF-2 in treatment of Crohn's disease in patients. They also present evidence that the role of the MAP kinases in the disease process is multifacetted. The implications in the use of p38 mitogen-activated protein kinase inhibitors such as CNI-1493 for treatment of Crohn's disease is discussed.
IT **164301-51-3**, CNI-1493
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(differential **p38** mitogen-activated protein kinase target phosphorylation in responders and nonresponders to infliximab in relation to therapeutic effect of inhibitors)
RN 164301-51-3 CAPLUS
CN Decanediamide, N,N'-bis[3,5-bis[1-[(aminoiminomethyl)hydrazono]ethyl]phenyl]-, tetrahydrochloride (9CI) (CA INDEX NAME)



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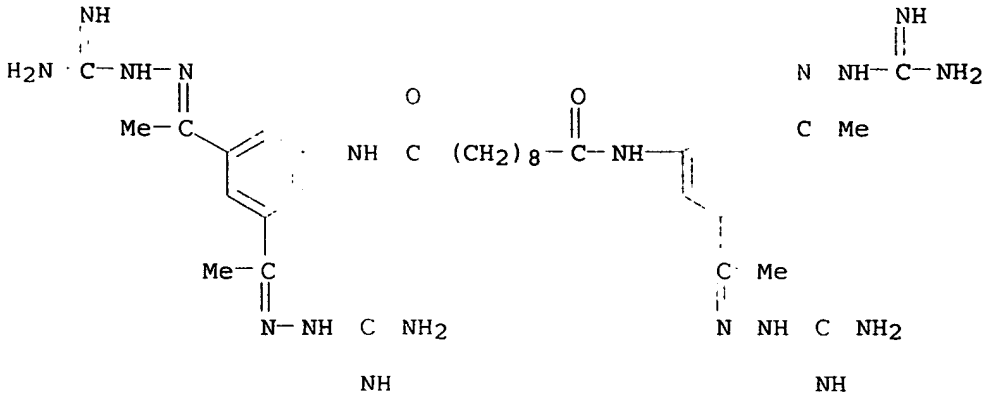
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:691318 CAPLUS
DN 140:104225
TI Review article: Mitogen-activated protein kinases in chronic intestinal inflammation - targeting ancient pathways to treat modern diseases
AU Waetzig, G. H.; Schreiber, S.
CS Mucosal Immunology Research Group, Department of General Internal Medicine, University Hospital Schleswig-Holstein, Kiel, Germany
SO Alimentary Pharmacology and Therapeutics (2003), 18(1), 17-32
CODEN: APTHEN; ISSN: 0269-2813
PB Blackwell Publishing Ltd.
DT Journal; General Review
LA English
AB A review. Conventional treatment of chronic inflammatory disorders, including inflammatory bowel diseases, employs broad-range antiinflammatory drugs. In order to reduce the side-effects and increase the efficacy of treatment, several strategies have been developed in the last decade to interfere with intercellular and intracellular inflammatory signaling processes. The highly conserved mitogen-activated protein kinase pathways regulate most cellular processes, particularly defense mechanisms such as stress reactions and inflammation. Here, we provide an overview of the current knowledge of the specificity and interconnection of mitogen-activated protein kinase pathways, their functions in the gut immune system and published and ongoing studies on the role of mitogen-activated protein kinases in inflammatory bowel disease. The development of mitogen-activated protein kinase inhibitors and their use for the therapy of inflammatory disorders is a paradigm of the successful bridging of the gap between basic research and clin. practice.
IT **164301-51-3**, CNI-1493
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mitogen-activated protein kinases in chronic intestinal inflammation and development of antiinflammatory **MAP kinase** inhibitors)
RN 164301-51-3 CAPLUS
CN Decanediamide, N,N'-bis[3,5-bis[1-[(aminoiminomethyl)hydrazono]ethyl]phenyl]-, tetrahydrochloride (9CI) (CA INDEX NAME)



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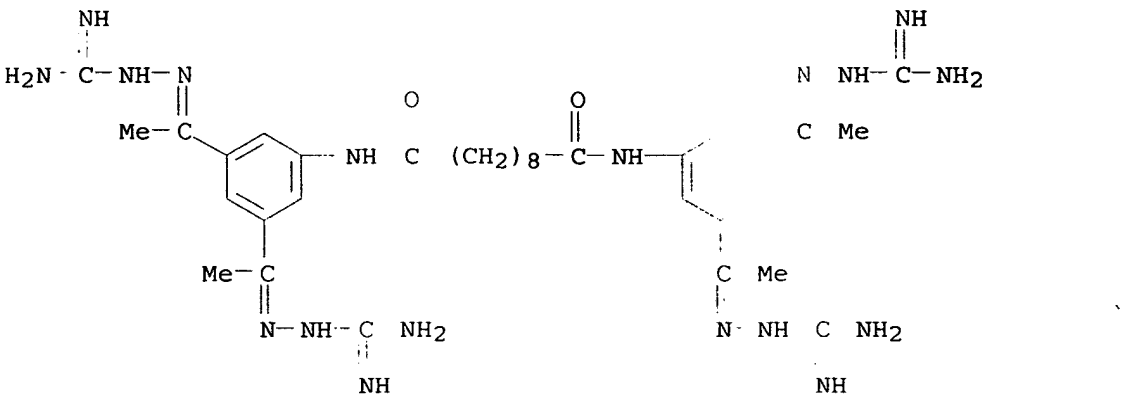
RE.CNT 167 THERE ARE 167 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:62440 CAPLUS
DN 136:256901
TI Inhibition of stress-activated MAP kinases induces clinical improvement in moderate to severe Crohn's disease
AU Hommes, Daan; Van Den Blink, Bernt; Plasse, Terry; Bartelsman, Joep; Xu, Cuiping; Macpherson, Bret; Tytgat, Guido; Peppelenbosch, Maikel; Van Deventer, Sander
CS Department of Gastroenterology and Hepatology, University of Amsterdam, Amsterdam, Neth.
SO Gastroenterology (2002), 122(1), 7-14
CODEN: GASTAB; ISSN: 0016-5085
PB W. B. Saunders Co.
DT Journal
LA English
AB Background & Aims: We investigated if inhibition of mitogen-activated protein kinases (MAPKs) was beneficial in Crohn's disease. Methods: Inhibition of JNK and p38 MAPK activation with CNI-1493, a guanylhydrazone, was tested in vitro. Twelve patients with severe Crohn's disease (mean baseline, CDAI 380) were randomly assigned to receive either 8 or 25 mg/m2 CNI-1493 daily for 12 days. Clin. endpoints included safety, Crohn's Disease Activity Index (CDAI), Inflammatory Bowel Disease Questionnaire, and the Crohn's Disease Endoscopic Index of Severity. Results: Colonic biopsies displayed enhanced JNK and p38 MAPK activation. CNI-1493 inhibition of both JNK and p38 phosphorylation was observed in vitro. Treatment resulted in diminished JNK phosphorylation and tumor necrosis factor production as well as significant clin. benefit and rapid endoscopic ulcer healing. No serious adverse events were noted. A CDAI decrease of 120 at week 4 (P = 0.005) and 146.5 at week 8 (P = 0.005) was observed A clin. response was seen in 67% of patients at 4 wk and 58% at 8 wk. Clin. remission was observed in 25% of patients at week 4 and 42% at week 8. Endoscopic improvement occurred in all but 1 patient. Response was seen in 3 of 6 infliximab failures, 2 of whom showed remission. Fistulae healing occurred in 4 of 5 patients, and steroids were tapered in 89% of patients. Conclusions: Inflammatory MAPKs are critically involved in the pathogenesis of Crohn's disease and their inhibition provides a novel therapeutic strategy.
IT **164301-51-3**, CNI-1493
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stress-activated **MAP** kinases inhibition with CNI-1493

induces clin. improvement in moderate to severe Crohn's disease)
RN 164301-51-3 CAPLUS
CN Decanediamide, N,N'-bis[3,5-bis[1-[(aminoiminomethyl)hydrazono]ethyl]phenyl]-, tetrahydrochloride (9CI) (CA INDEX NAME)



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RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

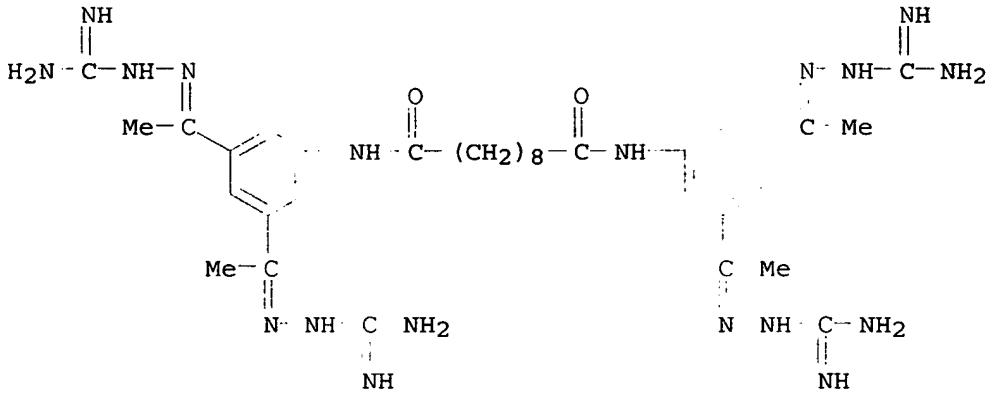
L11 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:716301 CAPLUS
DN 136:272686
TI Inhibition of p38 mitogen activate kinase attenuates the severity of pancreatitis-induced adult respiratory distress syndrome
AU Denham, Woody; Yang, Jun; Wang, Haichao; Botchkina, Galina; Tracey, Kevin J.; Norman, James
CS Department of Surgery, University of South Florida, Tampa, FL, 33612, USA
SO Critical Care Medicine (2000), 28(7), 2567-2572
CODEN: CCMDC7; ISSN: 0090-3493
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Adult respiratory distress syndrome (ARDS) is responsible for a significant portion of the morbidity and mortality during severe acute pancreatitis. Because inflammatory mediators such as tumor necrosis factor (TNF)-α and nitric oxide (NO) produced within the lungs have been implicated in sepsis-induced ARDS, the authors aimed to determine the role of these mediators in pancreatitis-induced ARDS using a model whereby ascites from animals with pancreatitis is transferred to otherwise healthy animals resulting in pulmonary injury. Sterile, endotoxin- and cytokine-free pancreatic ascites tested for interleukin (IL)-1β, TNF-α, interferon-γ, and IL-6 was obtained from rats 18 h after the induction of severe, acute pancreatitis. Ascites was subsequently administered i.v. (20 mL/kg) to healthy rats. Sham animals were administered i.v. saline. Healthy animals administered i.v. ascites were randomized to receive a single i.p. injection of the p38 mitogen activated kinase inhibitor CNI-1493 (1 mg/kg) or vehicle. Pulmonary injury was assessed at 24 h by histol. and leukocyte and protein concns. via bronchoalveolar lavage. Pulmonary TNF-α protein was detected by immunohistochem. Serum nitrite, as a measure of NO production, was measured utilizing the Griess reaction. After the i.v. administration of pancreatic ascites, the number of leukocytes and the protein concentration within the bronchoalveolar fluid were increased and pulmonary histol. was worsened consistent with acute lung injury (all vs. sham). Each of these

variables of pulmonary injury was lessened in animals receiving CNI-1493 and i.v. ascites (vs. vehicle). Pulmonary TNF-α protein and serum nitrites were decreased with the administration of CNI-1493 (vs. vehicle). A component of pancreatic ascites other than endotoxin, bacteria, or cytokines (IL-1β, TNF, interferon-γ, or IL-6) is capable of inducing ARDS in healthy animals. Inhibition of p38 mitogen activated kinase decreases the pulmonary injury through attenuated production of TNF-α and NO suggesting a primary role for these mediators in pancreatitis-induced ARDS.

IT **164301-51-3**, CNI-1493
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of **p38** mitogen activate kinase attenuates severity of pancreatitis-induced adult respiratory distress syndrome)

RN 164301-51-3 CAPLUS

CN Decanediamide, N,N'-bis[3,5-bis[1-[(aminoiminomethyl)hydrazono]ethyl]phenyl]-, tetrahydrochloride (9CI) (CA INDEX NAME)



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RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

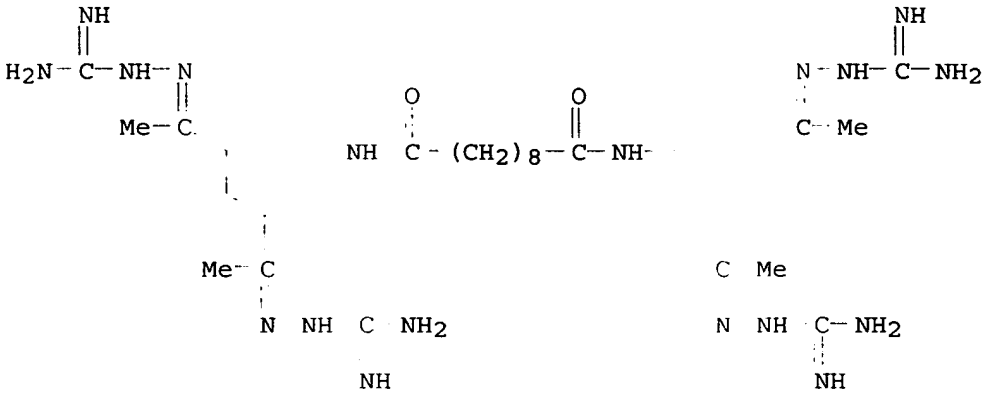
L11 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:119759 CAPLUS
DN 135:121136
TI CNI-1493 prevents induction of endotoxin tolerance by LPS pretreatment in RAW264.7 macrophages
AU Clair, Laurel; Heagy, Wyrta; Tracey, Kevin J.; Rodriguez, Jorge L.; West, Michael A.
CS Department of Surgery, University of Minnesota, Minneapolis, MN, USA
SO Surgical Forum (2000), 51, 223-225
CODEN: SUFOAX; ISSN: 0071-8041
PB American College of Surgeons
DT Journal
LA English
AB CNI-1493 is a tetravalent guanylhydrazone compound that blocks macrophage activation. A study was conducted to determine whether CNI-1493 could block development of endotoxin (LPS) tolerance. Results showed that macrophage inhibitor CNI-1493 prevented development of endotoxin tolerance. Although administration of CNI-1493 to naive macrophages prevented LPS-stimulated tumor necrosis factor (TNF) secretion, CNI-1493 before LPS pretreatment restored LPS-stimulated TNF secretion. It is hypothesized that CNI-1493 blocks the signal transduction pathway through which LPS pretreatment induces endotoxin tolerance. Since CNI-1493 has been shown to interfere with p38 kinase activation, this step may be important in development of

endotoxin tolerance. Thus, CNI-1493 may be a useful probe to understand the mechanisms of endotoxin tolerance and could be useful to prevent macrophage dysfunction in sepsis.

IT **164301-51-3**, CNI 1493
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(CNI-1493 prevents induction of endotoxin tolerance by LPS pretreatment in RAW264.7 macrophages via **p38** kinase inhibition)

RN 164301-51-3 CAPLUS

CN Decanediamide, N,N'-bis[3,5-bis[1-[(aminoiminomethyl)hydrazono]ethyl]phenyl]-, tetrahydrochloride (9CI) (CA INDEX NAME)



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RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
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             0 164301-51-3D
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                (164301-51-3 (NOTL) 164301-51-3D )

=> s l12 (L) HIV
         63471 HIV
L13          1 L12 (L) HIV

=> d bib abs hitstr
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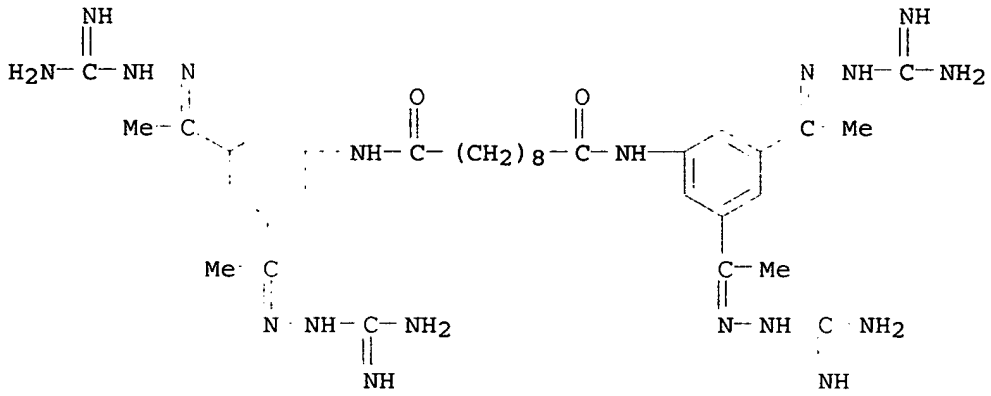
L13 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:221229 CAPLUS
DN 133:29514
TI Thermal hyperalgesia and mechanical allodynia produced by intrathecal administration of the human immunodeficiency virus-1 (HIV-1) envelope glycoprotein, gp120
AU Milligan, E. D.; Mehmert, K. K.; Hinde, J. L.; Harvey, L. O.; Martin, D.; Tracey, K. J.; Maier, S. F.; Watkins, L. R.
CS Department of Psychology, University of Colorado at Boulder, Boulder, CO, USA
SO Brain Research (2000), 861(1), 105-116
CODEN: BRREAP; ISSN: 0006-8993
PB Elsevier Science B.V.
DT Journal
LA English
AB Astrocytes and microglia in the spinal cord have recently been reported to

contribute to the development of peripheral inflammation-induced exaggerated pain states. Both lowering of thermal pain threshold (thermal hyperalgesia) and lowering of response threshold to light tactile stimuli (mech. allodynia) have been reported. The notion that spinal cord glia are potential mediators of such effects is based on the disruption of these exaggerated pain states by drugs thought to preferentially affect glial function. Activation of astrocytes and microglia can release many of the same substances that are known to mediate thermal hyperalgesia and mech. allodynia. The aim of the present series of studies was to determine whether exaggerated pain states could also be created in rats by direct, intraspinal immune activation of astrocytes and microglia. The immune stimulus used was peri-spinal (intrathecal, i.t.) application of the Human Immunodeficiency Virus type 1 (HIV-1) envelope glycoprotein, gp120. This portion of HIV-1 is known to bind to and activate microglia and astrocytes. Robust thermal hyperalgesia (tail-flick, TF, and Hargreaves tests) and mech. allodynia (von Frey and touch-evoked agitation tests) were observed in response to i.t. gp120. Heat denaturing of the complex protein structure of gp120 blocked gp120-induced thermal hyperalgesia. Lastly, both thermal hyperalgesia and mech. allodynia to i.t. gp120 were blocked by spinal pretreatment with drugs (fluorocitrate and CNI-1493) thought to preferentially disrupt glial function.

IT **164301-51-3**, Cni-1493
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thermal hyperalgesia and mech. allodynia produced by intrathecal administration of **HIV**-1 virus glycoprotein gp120 blocking by)

RN 164301-51-3 CAPLUS

CN Decanediamide, N,N'-bis[3,5-bis[1-[(aminoiminomethyl)hydrazono]ethyl]phenyl]-, tetrahydrochloride (9CI) (CA INDEX NAME)



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RE.CNT 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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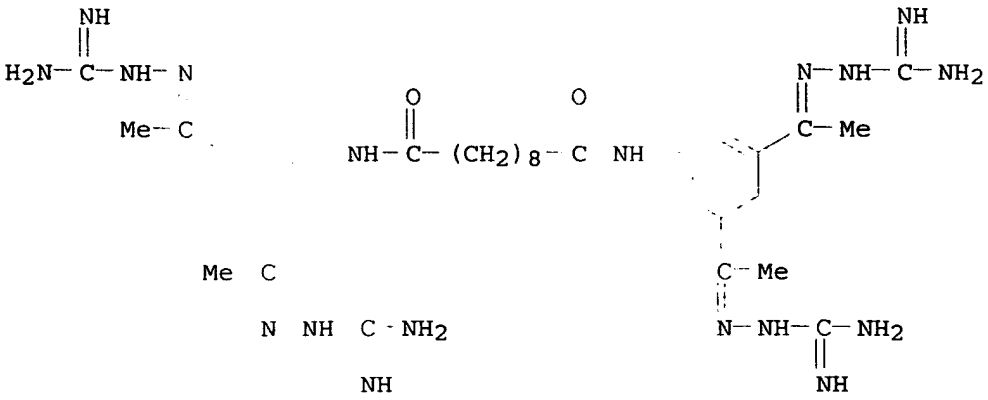
59 164301-51-3
0 164301-51-3D
L14 59 164301-51-3/RN
(164301-51-3 (NOTL) 164301-51-3D)

=> d 59 bib abs hitstr

L14 ANSWER 59 OF 59 CAPLUS COPYRIGHT 2005 ACS on STN

AN 1995:558462 CAPLUS
DN 123:25357
TI An inhibitor of macrophage arginine transport and nitric oxide production (CNI-1493) prevents acute inflammation and endotoxin lethality
AU Bianchi, Marina; Ulrich, Peter; Bloom, Ona; Meistrell, Malcolm III; Zimmerman, Gary A.; Schmidtmayerova, Helena; Bukrinsky, Michael; Donnelley, Thomas; Bucala, Richard; et al.
CS Picower Institute for Medical Research, Mannhasset, NY, 11030, USA
SO Molecular Medicine (Baltimore, MD, United States) (1995), 1(3), 254-66
CODEN: MOMEF3; ISSN: 1076-1551
DT Journal
LA English
AB Nitric oxide (NO), a small effector mol. produced enzymically from L-arginine by nitric oxide synthase (NOS), is a mediator not only of important homeostatic mechanisms (e.g., blood vessel tone and tissue perfusion), but also of key aspects of local and systemic inflammatory responses. Previous efforts to develop inhibitors of NOS to protect against NO-mediated tissue damage in endotoxin shock have been unsuccessful, largely because such competitive NOS antagonists interfere with critical vasoregulatory NO production in blood vessels and decrease survival in endotoxemic animals. Accordingly, we sought to develop a pharmaceutical approach to selectively inhibit NO production in macrophages while sparing NO responses in blood vessels. The processes of cytokine-inducible L-arginine transport and NO production were studied in the murine macrophage-like cell line (RAW 264.7). A series of multivalent guanylhydrazones were synthesized to inhibit cytokine-inducible L-arginine transport. One such compound (CNI-1493) was studied further in animal models of endothelial-derived relaxing factor (EDRF) activity, carrageenan inflammation, and lethal lipopolysaccharide (LPS) challenge. Upon activation with cytokines, macrophages increase transport of L-arginine to support the production of NO by NOS. Since endothelial cells do not require this addnl. arginine transport to produce NO, we reasoned that a competitive inhibitor of cytokine-inducible L-arginine transport would not inhibit EDRF activity in blood vessels, and thus might be effectively employed against endotoxic shock. CNI-1493, a tetravalent guanyl-hydrazone, proved to be a selective inhibitor of cytokine-inducible arginine transport and NO production, but did not inhibit EDRF activity. In mice, CNI-1493 prevented the development of carrageenan-induced footpad inflammation, and conferred protection against lethal LPS challenge. A selective inhibitor of cytokine-inducible L-arginine transport that does not inhibit vascular EDRF responses is effective against endotoxin lethality and significantly reduces inflammatory responses.
IT **164301-51-3**, CNI 1493
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitor of macrophage arginine transport and nitric oxide production (CNI-1493) prevents acute inflammation and endotoxin lethality)
RN 164301-51-3 CAPLUS
CN Decanediamide, N,N'-bis[3,5-bis[1-[(aminoiminomethyl)hydrazono]ethyl]phenyl]-, tetrahydrochloride (9CI) (CA INDEX NAME)



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         87554 "MAP"
        252214 "KINASE"
         16089 "MAP KINASE"
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         13262 "MAPK"
L15         14 L14 AND (HIV OR ("MAP" OR "MAP KINASE" OR "MAPK"))

=> d 10-14 bib abs hitstr
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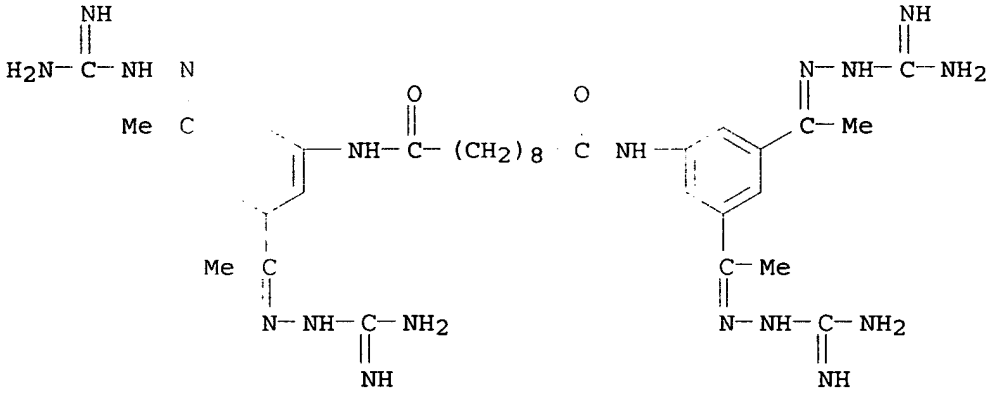
L15 ANSWER 10 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:62440 CAPLUS
DN 136:256901
TI Inhibition of stress-activated **MAP** kinases induces clinical improvement in moderate to severe Crohn's disease
AU Hommes, Daan; Van Den Blink, Bernt; Plasse, Terry; Bartelsman, Joep; Xu, Cuiping; Macpherson, Bret; Tytgat, Guido; Peppelenbosch, Maikel; Van Deventer, Sander
CS Department of Gastroenterology and Hepatology, University of Amsterdam, Amsterdam, Neth.
SO Gastroenterology (2002), 122(1), 7-14
CODEN: GASTAB; ISSN: 0016-5085
PB W. B. Saunders Co.
DT Journal
LA English
AB Background & Aims: We investigated if inhibition of mitogen-activated protein kinases (MAPKs) was beneficial in Crohn's disease. Methods: Inhibition of JNK and p38 **MAPK** activation with CNI-1493, a guanylhydrazone, was tested in vitro. Twelve patients with severe Crohn's disease (mean baseline, CDAI 380) were randomly assigned to receive either 8 or 25 mg/m2 CNI-1493 daily for 12 days. Clin. endpoints included safety, Crohn's Disease Activity Index (CDAI), Inflammatory Bowel Disease Questionnaire, and the Crohn's Disease Endoscopic Index of Severity. Results: Colonic biopsies displayed enhanced JNK and p38 **MAPK** activation. CNI-1493 inhibition of both JNK and p38 phosphorylation was observed in vitro. Treatment resulted in diminished JNK phosphorylation and tumor necrosis factor production as well as significant clin. benefit and rapid endoscopic ulcer healing. No serious adverse events were noted. A CDAI decrease of 120 at week 4 (P = 0.005) and 146.5 at week 8 (P = 0.005) was observed A clin. response was seen in 67% of patients at 4 wk and 58% at

8 wk. Clin. remission was observed in 25% of patients at week 4 and 42% at week 8. Endoscopic improvement occurred in all but 1 patient. Response was seen in 3 of 6 infliximab failures, 2 of whom showed remission. Fistulae healing occurred in 4 of 5 patients, and steroids were tapered in 89% of patients. Conclusions: Inflammatory MAPKs are critically involved in the pathogenesis of Crohn's disease and their inhibition provides a novel therapeutic strategy.

IT **164301-51-3**, CNI-1493
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stress-activated **MAP** kinases inhibition with CNI-1493 induces clin. improvement in moderate to severe Crohn's disease)

RN 164301-51-3 CAPLUS

CN Decanediamide, N,N'-bis[3,5-bis[1-[(aminoiminomethyl)hydrazono]ethyl]phenyl]-, tetrahydrochloride (9CI) (CA INDEX NAME)



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RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN

AN 2001:716301 CAPLUS

DN 136:272686

TI Inhibition of p38 mitogen activate kinase attenuates the severity of pancreatitis-induced adult respiratory distress syndrome

AU Denham, Woody; Yang, Jun; Wang, Haichao; Botchkina, Galina; Tracey, Kevin J.; Norman, James

CS Department of Surgery, University of South Florida, Tampa, FL, 33612, USA

SO Critical Care Medicine (2000), 28(7), 2567-2572
CODEN: CCMDC7; ISSN: 0090-3493

PB Lippincott Williams & Wilkins

DT Journal

LA English

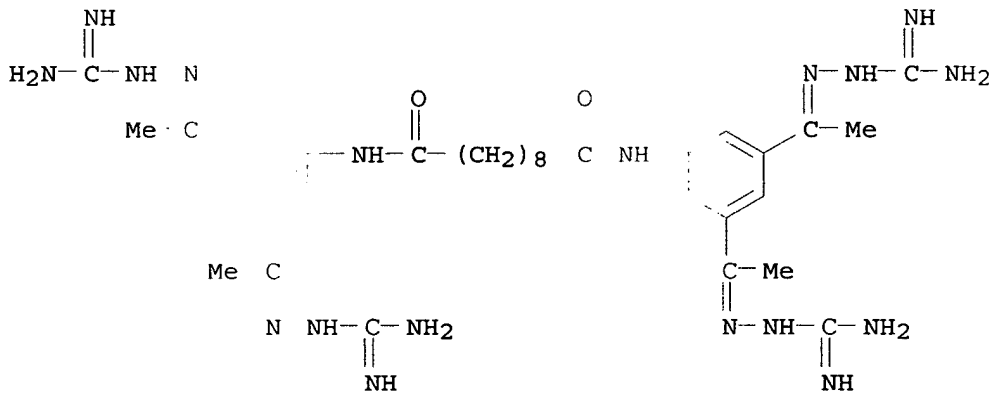
AB Adult respiratory distress syndrome (ARDS) is responsible for a significant portion of the morbidity and mortality during severe acute pancreatitis. Because inflammatory mediators such as tumor necrosis factor (TNF)-α and nitric oxide (NO) produced within the lungs have been implicated in sepsis-induced ARDS, the authors aimed to determine the role of these mediators in pancreatitis-induced ARDS using a model whereby ascites from animals with pancreatitis is transferred to otherwise healthy animals resulting in pulmonary injury. Sterile, endotoxin- and cytokine-free pancreatic ascites tested for interleukin (IL)-1β, TNF-α, interferon-γ, and IL-6 was obtained from rats 18 h after the induction of severe, acute pancreatitis. Ascites was subsequently administered i.v. (20 mL/kg) to healthy rats. Sham animals

were administered i.v. saline. Healthy animals administered i.v. ascites were randomized to receive a single i.p. injection of the p38 mitogen activated kinase inhibitor CNI-1493 (1 mg/kg) or vehicle. Pulmonary injury was assessed at 24 h by histol. and leukocyte and protein concns. via bronchoalveolar lavage. Pulmonary TNF-α protein was detected by immunohistochem. Serum nitrite, as a measure of NO production, was measured utilizing the Griess reaction. After the i.v. administration of pancreatic ascites, the number of leukocytes and the protein concentration within the bronchoalveolar fluid were increased and pulmonary histol. was worsened consistent with acute lung injury (all vs. sham). Each of these variables of pulmonary injury was lessened in animals receiving CNI-1493 and i.v. ascites (vs. vehicle). Pulmonary TNF-α protein and serum nitrites were decreased with the administration of CNI-1493 (vs. vehicle). A component of pancreatic ascites other than endotoxin, bacteria, or cytokines (IL-1β, TNF, interferon-γ, or IL-6) is capable of inducing ARDS in healthy animals. Inhibition of p38 mitogen activated kinase decreases the pulmonary injury through attenuated production of TNF-α and NO suggesting a primary role for these mediators in pancreatitis-induced ARDS.

IT **164301-51-3**, CNI-1493
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of p38 mitogen activate kinase attenuates severity of pancreatitis-induced adult respiratory distress syndrome)

RN 164301-51-3 CAPLUS

CN Decanediamide, N,N'-bis[3,5-bis[1-[(aminoiminomethyl)hydrazono]ethyl]phenyl]-, tetrahydrochloride (9CI) (CA INDEX NAME)



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RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN

AN 2000:221229 CAPLUS

DN 133:29514

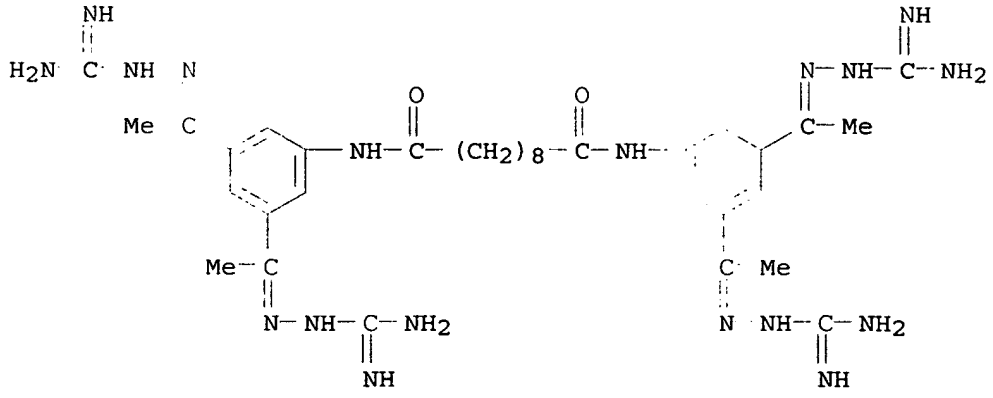
TI Thermal hyperalgesia and mechanical allodynia produced by intrathecal administration of the human immunodeficiency virus-1 (**HIV**-1) envelope glycoprotein, gp120

AU Milligan, E. D.; Mehmert, K. K.; Hinde, J. L.; Harvey, L. O.; Martin, D.; Tracey, K. J.; Maier, S. F.; Watkins, L. R.

CS Department of Psychology, University of Colorado at Boulder, Boulder, CO, USA

SO Brain Research (2000), 861(1), 105-116
CODEN: BRREAP; ISSN: 0006-8993

PB Elsevier Science B.V.
DT Journal
LA English
AB Astrocytes and microglia in the spinal cord have recently been reported to contribute to the development of peripheral inflammation-induced exaggerated pain states. Both lowering of thermal pain threshold (thermal hyperalgesia) and lowering of response threshold to light tactile stimuli (mech. allodynia) have been reported. The notion that spinal cord glia are potential mediators of such effects is based on the disruption of these exaggerated pain states by drugs thought to preferentially affect glial function. Activation of astrocytes and microglia can release many of the same substances that are known to mediate thermal hyperalgesia and mech. allodynia. The aim of the present series of studies was to determine whether exaggerated pain states could also be created in rats by direct, intraspinal immune activation of astrocytes and microglia. The immune stimulus used was peri-spinal (intrathecal, i.t.) application of the Human Immunodeficiency Virus type 1 (**HIV**-1) envelope glycoprotein, gp120. This portion of **HIV**-1 is known to bind to and activate microglia and astrocytes. Robust thermal hyperalgesia (tail-flick, TF, and Hargreaves tests) and mech. allodynia (von Frey and touch-evoked agitation tests) were observed in response to i.t. gp120. Heat denaturing of the complex protein structure of gp120 blocked gp120-induced thermal hyperalgesia. Lastly, both thermal hyperalgesia and mech. allodynia to i.t. gp120 were blocked by spinal pretreatment with drugs (fluorocitrate and CNI-1493) thought to preferentially disrupt glial function.
IT **164301-51-3**, Cni-1493
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thermal hyperalgesia and mech. allodynia produced by intrathecal administration of **HIV**-1 virus glycoprotein gp120 blocking by)
RN 164301-51-3 CAPLUS
CN Decanediamide, N,N'-bis[3,5-bis[1-[(aminoiminomethyl)hydrazono]ethyl]phenyl]-, tetrahydrochloride (9CI) (CA INDEX NAME)



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RE.CNT 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 13 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:338118 CAPLUS
DN 129:36435
TI Guanylhydrazones useful for treating diseases associated with T-cell activation
IN Tracey, Kevin; Cohen, Pamela; Bukrinsky, Michael; Schmidtmayerova, Helena

PA Picower Institute for Medical Research, USA
SO PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9820868	A1	19980522	WO 1997-US20670	19971114
	W: AL, AU, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IL, IS, JP, KR, KZ, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SI, SK, TR, UA, UZ, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2271693	AA	19980522	CA 1997-2271693	19971114
	AU 9854360	A1	19980603	AU 1998-54360	19971114
	AU 746647	B2	20020502		
	EP 963197	A1	19991215	EP 1997-948263	19971114
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
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	JP 2001503775	T2	20010321	JP 1998-522801	19971114
	US 6673777	B1	20040106	US 2000-705581	20001102
	US 2004171695	A1	20040902	US 2003-619426	20030716
PRAI	US 1996-31061P	P	19961115		
	US 1997-970973	A3	19971114		
	WO 1997-US20670	W	19971114		
	US 2000-705581	A1	20001102		

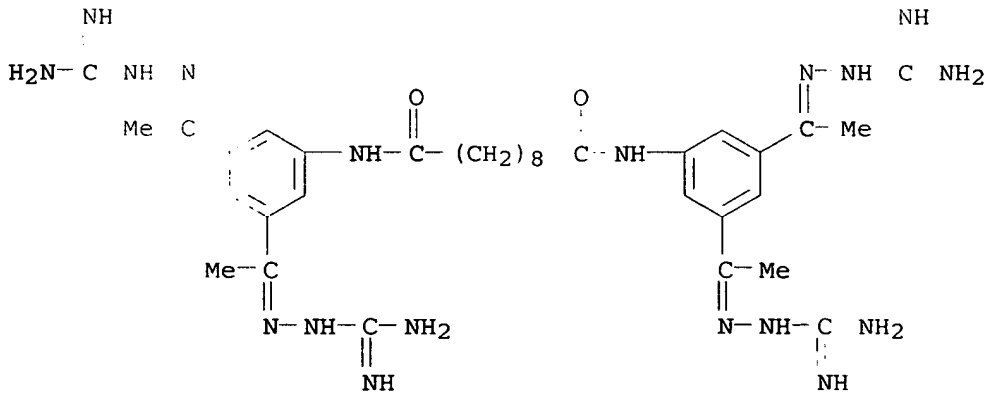
OS MARPAT 129:36435

AB There is disclosed a method for treating diseases and disorders involving T-cell activation and **HIV**-infection, using the p38 mitogen-activated protein kinase (**MAPK**) signaling pathway as a target for intervention. There is further disclosed a use for guanylhydrazone-substituted compds. to treat diseases and disorders related to T cell activation and **HIV**-infection.

IT **164301-51-3**, CNI-1493
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(guanylhydrazones useful for treating diseases associated with T-cell activation)

RN 164301-51-3 CAPLUS

CN Decanediamide, N,N'-bis[3,5-bis[1-[(aminoiminomethyl)hydrazono]ethyl]phenyl]-, tetrahydrochloride (9CI) (CA INDEX NAME)



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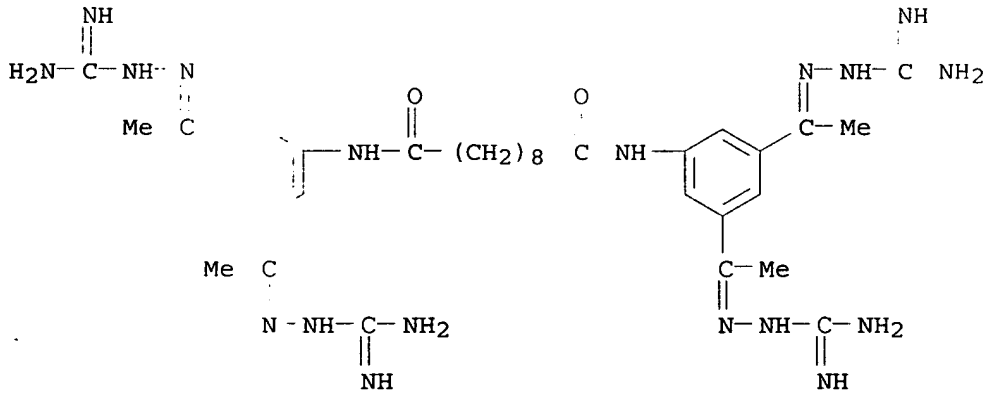
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 14 OF 14 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:229945 CAPLUS
DN 129:36244
TI Specific inhibition of macrophage-derived proinflammatory cytokine synthesis with a tetravalent guanylhydrazone CNI-1493 accelerates early islet graft function posttransplant
AU Hyon, S. H.; Tracey, K. J.; Kaufman, D. B.
CS Div. Transplantation, Northwest. Univ. Med. Sch., Chicago, IL, USA
SO Transplantation Proceedings (1998), 30(2), 409-410
CODEN: TRPPA8; ISSN: 0041-1345
PB Elsevier Science Inc.
DT Journal
LA English
AB The effects of CNI-1493, a potent inhibitor of macrophage-derived proinflammatory cytokine production and the p38 **MAP kinase** signal transduction pathway, were studied in streptozotocin-induced diabetic mice that received pancreatic islet isografts. CNI-1493 treatment of recipient mice significantly shortened the duration of posttransplantation hyperglycemia following islet transplantation. CNI-1493 reduced host tumor necrosis factor levels following islet transplantation. These observations are consistent with the hypothesis that CNI-1493 suppresses the inhibitory effects on islet function exerted by temporary, nonspecific inflammatory mediators induced during the early phase of transplantation. Interference with the p38 **MAP kinase** signal transduction pathway appears to be an effective method of inhibiting hose macrophage activity involving proinflammatory cytokine synthesis. This new approach of host immunosuppression may have applicability in the field of islet transplantation.
IT **164301-51-3**, CNI-1493
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(inhibition of macrophage-derived proinflammatory cytokine synthesis with CNI-1493 accelerates early pancreatic islet graft function)
RN 164301-51-3 CAPLUS
CN Decanediamide, N,N'-bis[3,5-bis[1-[(aminoiminomethyl)hydrazono]ethyl]phenyl]-, tetrahydrochloride (9CI) (CA INDEX NAME)



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RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L16           9 L14 AND VIRUS

=> d 8-9 bib abs hitstr

L16  ANSWER 8 OF 9  CAPLUS  COPYRIGHT 2005 ACS on STN
AN   2000:221229  CAPLUS
DN   133:29514
TI   Thermal hyperalgesia and mechanical allodynia produced by intrathecal
     administration of the human immunodeficiency virus-1 (HIV-1)
     envelope glycoprotein, gp120
AU   Milligan, E. D.; Mehmert, K. K.; Hinde, J. L.; Harvey, L. O.; Martin, D.;
     Tracey, K. J.; Maier, S. F.; Watkins, L. R.
CS   Department of Psychology, University of Colorado at Boulder, Boulder, CO,
     USA
SO   Brain Research (2000), 861(1), 105-116
     CODEN: BRREAP; ISSN: 0006-8993
PB   Elsevier Science B.V.
DT   Journal
LA   English
AB   Astrocytes and microglia in the spinal cord have recently been reported to
     contribute to the development of peripheral inflammation-induced
     exaggerated pain states.  Both lowering of thermal pain threshold (thermal
     hyperalgesia) and lowering of response threshold to light tactile stimuli
     (mech. allodynia) have been reported.  The notion that spinal cord glia
     are potential mediators of such effects is based on the disruption of
     these exaggerated pain states by drugs thought to preferentially affect
     glial function.  Activation of astrocytes and microglia can release many
     of the same substances that are known to mediate thermal hyperalgesia and
     mech. allodynia.  The aim of the present series of studies was to determine
     whether exaggerated pain states could also be created in rats by direct,
     intraspinal immune activation of astrocytes and microglia.  The immune
     stimulus used was peri-spinal (intrathecal, i.t.) application of the Human
     Immunodeficiency Virus type 1 (HIV-1) envelope glycoprotein,
     gp120.  This portion of HIV-1 is known to bind to and activate microglia
     and astrocytes.  Robust thermal hyperalgesia (tail-flick, TF, and
     Hargreaves tests) and mech. allodynia (von Frey and touch-evoked agitation
     tests) were observed in response to i.t. gp120.  Heat denaturing of the
     complex protein structure of gp120 blocked gp120-induced thermal
     hyperalgesia.  Lastly, both thermal hyperalgesia and mech. allodynia to
     i.t. gp120 were blocked by spinal pretreatment with drugs (fluorocitrate
     and CNI-1493) thought to preferentially disrupt glial function.
IT   164301-51-3, Cni-1493
     RL: BAC (Biological activity or effector, except adverse); BSU (Biological
     study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
     (Uses)
        (thermal hyperalgesia and mech. allodynia produced by intrathecal
        administration of HIV-1 virus glycoprotein gp120 blocking by)
RN   164301-51-3  CAPLUS
CN   Decanediamide, N,N'-bis[3,5-bis[1-[(aminoiminomethyl)hydrazono]ethyl]pheny
     l]-, tetrahydrochloride (9CI)  (CA INDEX NAME)
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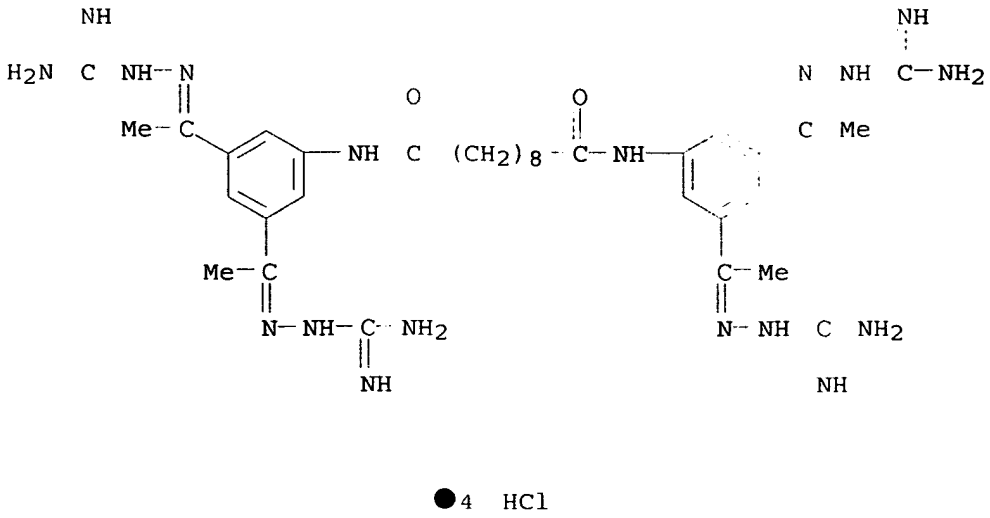

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RE.CNT 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:338118 CAPLUS
DN 129:36435
TI Guanylhydrazones useful for treating diseases associated with T-cell activation
IN Tracey, Kevin; Cohen, Pamela; Bukrinsky, Michael; Schmidtmayerova, Helena
PA Picower Institute for Medical Research, USA
SO PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9820868	A1	19980522	WO 1997-US20670	19971114
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	RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2271693	AA	19980522	CA 1997-2271693	19971114
	AU 9854360	A1	19980603	AU 1998-54360	19971114
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	EP 963197	A1	19991215	EP 1997-948263	19971114
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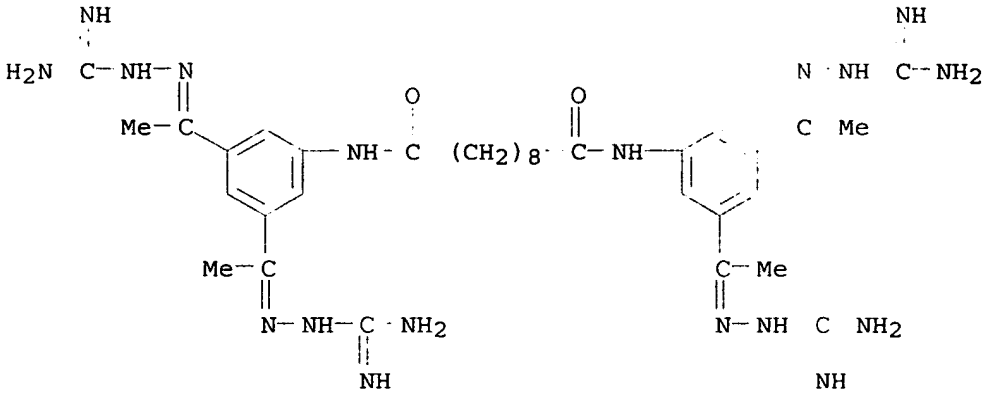
	US 6673777	B1	20040106	US 2000-705581	20001102
	US 2004171695	A1	20040902	US 2003-619426	20030716
PRAI	US 1996-31061P	P	19961115		
	US 1997-970973	A3	19971114		
	WO 1997-US20670	W	19971114		
	US 2000-705581	A1	20001102		

OS MARPAT 129:36435
AB There is disclosed a method for treating diseases and disorders involving T-cell activation and HIV-infection, using the p38 mitogen-activated protein kinase (MAPK) signaling pathway as a target for intervention. There is further disclosed a use for guanylhydrazone-substituted compds. to treat diseases and disorders related to T cell activation and HIV-infection.

IT **164301-51-3**, CNI-1493
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(guanylhydrazones useful for treating diseases associated with T-cell activation)
RN 164301-51-3 CAPLUS
CN Decanediamide, N,N'-bis[3,5-bis[1-[(aminoiminomethyl)hydrazono]ethyl]phenyl]-, tetrahydrochloride (9CI) (CA INDEX NAME)



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RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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59 164301-51-3
0 164301-51-3D
L17 59 164301-51-3/RN
(164301-51-3 (NOTL) 164301-51-3D)

=> d 50-58 bib abs

L17 ANSWER 50 OF 59 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1997:605040 CAPLUS
DN 127:257172
TI Protection against lethal polymicrobial sepsis by CNI-1493, an inhibitor of pro-inflammatory cytokine synthesis
AU Villa, P.; Meazza, C.; Sironi, M.; Bianchi, M.; Ulrich, P.; Botchkina, G.; Tracey, K. J.; Ghezzi, P.
CS Mario Negri Institute for Pharmacological Research, Milan, Italy
SO Journal of Endotoxin Research (1997), 4(3), 197-204
CODEN: JENREB; ISSN: 0968-0519
PB Churchill Livingstone
DT Journal
LA English
AB Polymicrobial sepsis caused by cecal ligation and puncture (CLP) in mice produces the inflammatory and pathol. sequelae of lung neutrophil infiltration, adult respiratory distress syndrome (ARDS), and death. These sequelae are dependent upon the synergistic interaction between several inflammatory mediators, including tumor necrosis factor (TNF), interleukin 1 (IL-1), and nitric oxide (NO). The overlapping spectrum of multiple mediator toxicity has hampered efforts to develop therapies for sepsis based on selective inhibition of a single mediator. Therefore, the authors tested the hypothesis that inhibition of multiple pro-inflammatory

mediators would abrogate lethality. The results show that administration of a tetravalent guanylhydrazone compound (CNI-1493) protected mice against 10 day mortality in CLP. Evidence of suppression of the cytokine cascade was given by decreased serum levels of TNF and IL-6 in CNI-1493 treated animals (TNF reduced 60% as compared to controls; IL-6 reduced 90% compared to controls), and decreased levels of the acute-phase protein serum amyloid A response measured 24 h after CLP. Serum nitrites/nitrates, which give an index of NO production, were also reduced (50%). Protection against CLP induced lung damage was observed as attenuation of edema and alveolar neutrophil infiltration, suppression of pulmonary TNF levels, and reduction of TUNEL-pos. staining in lung. Thus, CNI-1493 effectively inhibits the synthesis of multiple pro-inflammatory mediators and protects against death during polymicrobial sepsis.

RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 51 OF 59 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1997:124926 CAPLUS
DN 126:211914
TI Preparation of arylamidinohydrazones for treatment of cachexia and nitric oxide-mediated diseases.
IN Bianchi, Marina; Cerami, Anthony; Tracey, Kevin J.; Ulrich, Peter
PA Picower Institute for Medical Research, USA
SO U.S., 42 pp., Cont.-in-part of U.S. Ser. No. 184,540, abandoned.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5599984	A	19970204	US 1994-315170	19940929
	CA 2181689	AA	19950727	CA 1995-2181689	19950119
	WO 9519767	A1	19950727	WO 1995-US828	19950119
	W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, UZ, VN				
	RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9518330	A1	19950808	AU 1995-18330	19950119
	AU 683999	B2	19971127		
	EP 746312	A1	19961211	EP 1995-910110	19950119
	EP 746312	B1	20020925		
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	CN 1144480	A	19970305	CN 1995-192171	19950119
	CN 1098070	B	20030108		
	JP 09508123	T2	19970819	JP 1995-519690	19950119
	NZ 330610	A	20010727	NZ 1995-330610	19950119
	EP 1160240	A1	20011205	EP 2001-112374	19950119
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE				
	AT 224707	E	20021015	AT 1995-910110	19950119
	PT 746312	T	20030228	PT 1995-910110	19950119
	NZ 511951	A	20030328	NZ 1995-511951	19950119
	ES 2188651	T3	20030701	ES 1995-910110	19950119
	US 5750573	A	19980512	US 1995-463568	19950605
	US 5753684	A	19980519	US 1995-471696	19950606
	US 5849794	A	19981215	US 1995-472004	19950606
	US 5859062	A	19990112	US 1995-471124	19950606
	US 6008255	A	19991228	US 1995-471305	19950606
	US 6022900	A	20000208	US 1995-471919	19950606
	US 6180676	B1	20010130	US 1995-472003	19950606
	US 6248787	B1	20010619	US 1995-479050	19950606
	US 5854289	A	19981229	US 1996-632305	19960415
	US 2002028851	A1	20020307	US 2001-824217	20010403
PRAI	US 1994-184540	B2	19940121		

	US 1994-315170	A	19940929
	EP 1995-910110	A3	19950119
	NZ 1995-281400	A1	19950119
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	US 1995-463568	A3	19950605
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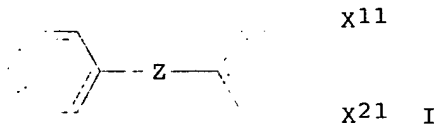
OS MARPAT 126:211914
GI



I

AB Title compds., e.g. [I; X2 = H, Q1, Q2; X1, X11, X21 = Q1, Q2; Z = NHCONH, C6H4, C5NH3, A(CH2)nA; n = 2-10; A = NHCO, NHCONH, NH, O; Q1 = H2N(CNH)NHN:CH, H2N(CNH)NHN:CMe], were prepared Thus, N,N'-bis(3,5-diacetylphenyl)decanediamide (preparation given), aminoguanidine hydrochloride, and aminoguanidine dihydrochloride were heated in EtOH for 18 h to give N,N'-bis(3,5-diacetylphenyl)decanediamide tetrakis(amidinohydrazone) tetrahydrochloride. The latter at 200 μM gave 100% inhibition of urea production, NO2/NO3 production, and arginine transport in activated macrophages.

L17 ANSWER 52 OF 59 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1996:723238 CAPLUS
DN 126:1075
TI A novel inhibitor of inflammatory cytokine production (CNI-1493) is cerebroprotective in permanent focal cerebral ischemia
AU Cockroft, Kevin M.; Meistrell, Malcolm; Ulrich, Peter; Cerami, Anthony; Tracey, Kevin J.
CS North Shore University Hospital, New York Hospital, Manhasset, NY, USA
SO Surgical Forum (1996), 47, 568-570
CODEN: SUFOAX; ISSN: 0071-8041
PB American College of Surgeons
DT Journal
LA English
AB We recently developed CNI-1493 as a potent and effective low-mol.-weight inhibitor of TNF synthesis. Although it is clear that TNF is produced by neurons in the ischemic penumbra and that TNF can activate secondary cytotoxicity cascades, the role of low-mol.-weight TNF inhibitors in stroke is unknown. The data presented here indicate that CNI-1493 effectively inhibits the development of stroke.

L17 ANSWER 53 OF 59 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1996:723205 CAPLUS
DN 126:731
TI An inhibitor of macrophage proinflammatory cytokines and nitric oxide production (CNI-1493) prolongs graft life in transplanted rat hearts
AU Minanov, Oktavijan P.; Ma, Ningsheng; Yang, Xiaochun; Ulrich, Peter; Tracey, Kevin J.; Cannon, Paul J.; Michler, Robert E.
CS College Physicians and Surgeons, Columbia University, New York, NY, USA
SO Surgical Forum (1996), 47, 418-420
CODEN: SUFOAX; ISSN: 0071-8041
PB American College of Surgeons
DT Journal
LA English
AB Since it appears that activated macrophages through the production of inducible nitric oxide synthase (iNOS), tumor necrosis factor, and

interleukin-1 can lead to allograft injury and that CNI-1493 selectively inhibits these macrophage products without interfering with the homeostatic mechanisms of cNOS, the authors tested the hypothesis that CNI-1493 could prolong graft life in a rat model of acute cardiac allograft rejection.

L17 ANSWER 54 OF 59 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1996:723155 CAPLUS
DN 126:929
TI A low molecular weight macrophage inhibitor decreases severity of pancreatitis through inhibition of IL-1 and TNF production
AU Fink, Gregory; Yang, Jun; Carter, Gay; Ward, Kristina; Ulrich, Peter; Tracey, Kevin; Norman, James
CS Department Surgery, University South Florida, Tampa, FL, USA
SO Surgical Forum (1996), 47, 137-140
CODEN: SUFOAX; ISSN: 0071-8041
PB American College of Surgeons
DT Journal
LA English
AB Administration of the organic mol. CNI-1493 to 2 distinct murine models of pancreatitis significantly lessened pancreatitis-induced intrapancreatic and intrapulmonary cytokine gene expression. This was associated with attenuated pancreatic damage and a decreased release of pancreatic enzymes into the serum that was not model dependent. This serves to confirm the role of inflammatory cytokines in the progression of pancreatitis and for the 1st time demonstrates that a small mol. can improve the severity of this disease through attenuation of the cytokine cascade.

L17 ANSWER 55 OF 59 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1996:286869 CAPLUS
DN 124:332241
TI CNI-1493 inhibits monocyte/macrophage tumor necrosis factor by suppression of translation efficiency
AU Cohen, Pamela S.; Nakshatri, Harikrishna; Dennis, Jameel; Caragine, Theresa; Bianchi, Marina; Cerami, Anthony; Tracey, Kevin J.
CS Lab. Biomed. Sci., Picower Inst. Med. Res., Manhasset, NY, 11030, USA
SO Proceedings of the National Academy of Sciences of the United States of America (1996), 93(9), 3967-3971
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
AB Tumor necrosis factor (TNF) mediates a wide variety of disease states including septic shock, acute and chronic inflammation, and cachexia. Recently, a multivalent guanylhydrazone (CNI-1493) developed as an inhibitor of macrophage activation was shown to suppress TNF production and protect against tissue inflammation and endotoxin lethality [Bianchi, M., Ulrich, P., Bloom, O., Meistrell, M., Zimmerman, G. a., Schmidtmayerova, H., Bukrinsky, M., Donnelley, T., Bucala, R., Sherry, B., Manogue, K. R., Tortolani, A. J., Cerami, A. & Tracey, K. J. (1995) Mol. Med. 1, 254-266, and Bianchi, M., bloom, O., Raabe, T., Cohen, P. S., Chesney, J., Sherry, B., Schmidtmayerova, H., Zhang, X., Bukrinsky, M., Ulrich, P., Cerami, A. & Tracey, J. (1996) J. Exp. Med., in press]. The authors have now elucidated the mechanism by which CNI-1493 inhibits macrophage TNF synthesis and show here that it acts through suppression of TNF translation efficiency. CNI-1493 blocked neither the lipopolysaccharide (LPS)-induced increases in the expression of TNF mRNA nor the translocation of nuclear factor NF-κB to the nucleus in macrophages activated by 15 min of LPS stimulation, indicating that CNI-1493 does not interfere with early NF-κB-mediated transcriptional regulation of TNF. However, synthesis of the 26-kDa membrane form of TNF was effectively blocked by CNI-1493. Further evidence for the translational suppression of TNF is given by expts. using chloramphenicol acetyltransferase (CAT) constructs containing elements of the TNF gene that are involved in TNF translational regulation. Both the 5' and 3'

untranslated regions of the TNF gene were required to elicit maximal translational suppression by CNI-1493. Identification of the mol. target through which CNI-1493 inhibits TNF translation should provide insight into the regulation of macrophage activation and mechanisms of inflammation.

L17 ANSWER 56 OF 59 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1996:189901 CAPLUS
DN 124:278442
TI Suppression of proinflammatory cytokines in monocytes by a tetravalent guanylhydrazone
AU Bianchi, Marina; Bloom, Ona; Raabe, Tobias; Cohen, Pamela S.; Chesney, Jason; Sherry, Barbara; Schmidtmayerova, Helena; Calandra, Thierry; Zhang, Xini; et al.
CS Lab. Biomed. Sci., North Shore Univ. Hosp., Manhasset, NY, 11030, USA
SO Journal of Experimental Medicine (1996), 183(3), 927-36
CODEN: JEMEAV; ISSN: 0022-1007
PB Rockefeller University Press
DT Journal
LA English
AB An overprodn. of proinflammatory cytokines by activated macrophages/monocytes mediates the injurious sequelae of inflammation, septic shock, tissue injury, and cachexia. We recently synthesized a tetravalent guanylhydrazone compound (CNI-1493) that inhibits cytokine-inducible arginine transport and nitric oxide (NO) production in macrophages, and protects mice against lethal endotoxemia and carrageenan-induced inflammation. During these investigations we noticed that CNI-1493 effectively prevented lipopolysaccharide (LPS)-induced NO production, even when added in concns. 10-fold less than required to competitively inhibit L-arginine uptake, suggesting that the suppressive effects of this guanylhydrazone compound might extend to other LPS-induced responses. Here, we report that CNI-1493 suppressed the LPS-stimulated production of proinflammatory cytokines (tumor necrosis factor [TNF], interleukins 1β and 6, macrophage inflammatory proteins 1α and 1 β) from human peripheral blood mononuclear cells. Cytokine suppression was specific, in that CNI-1493 did not inhibit either the constitutive synthesis of transforming growth factor β or the upregulation of major histocompatibility complex class II by interferon γ (IFN-γ). In contrast to the macrophage suppressive actions of dexamethasone, which are overridden in the presence of IFN-γ, CNI-1493 retained its suppressive effects even in the presence of IFN-γ. The mechanism of cytokine-suppressive action by CNI-1493 was independent of extracellular L-arginine content and NO production and is not restricted to induction by LPS. As a selective inhibitor of macrophage activation that prevents TNF production, this tetravalent guanylhydrazone could be useful in the development of cytokine-suppressive agents for the treatment of diseases mediated by overprodn. of cytokines.

L17 ANSWER 57 OF 59 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1996:77001 CAPLUS
DN 124:193144
TI High-performance liquid chromatographic method for guanylhydrazone compounds
AU Cerami, Carla; Zhang, Xini; Ulrich, Peter; Bianchi, Marina; Tracey, Kevin J.; Berger, Bradley J.
CS The Picower Institute for Medical Research, 350 Community Dr., Manhasset, NY, 11030, USA
SO Journal of Chromatography, B: Biomedical Applications (1996), 675(1), 71-5
CODEN: JCBBEP; ISSN: 0378-4347
PB Elsevier
DT Journal
LA English
AB A high-performance liquid chromatog. method has been developed for a series of aromatic guanylhydrazones that have demonstrated therapeutic potential as anti-inflammatory agents. The compds. were separated using octadecyl or

diisopropyloctyl reversed-phase columns, with an acetonitrile gradient in water containing heptane sulfonate, tetramethylammonium chloride, and phosphoric acid. The method was used to reliably quantify levels of analyte as low as 785 ng/mL, and the detector response was linear to at least 50 μg/mL, using a 100 μl injection volume The assay system was used to determine the basic pharmacokinetics of a lead compound, CNI-1493, from serum concns. following a single i.v. injection in rats.

L17 ANSWER 58 OF 59 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1995:896314 CAPLUS
DN 123:276077
TI Guanylhydrazones for treating cachexia and inflammatory and other conditions
IN Bianchi, Marina; Cerami, Anthony; Tracey, Kevin J.; Ulrich, Peter
PA Picower Institute for Medical Research, USA
SO PCT Int. Appl., 87 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9519767	A1	19950727	WO 1995-US828	19950119
	W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KE, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, UZ, VN				
	RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 5599984	A	19970204	US 1994-315170	19940929
	AU 9518330	A1	19950808	AU 1995-18330	19950119
	AU 683999	B2	19971127		
	EP 746312	A1	19961211	EP 1995-910110	19950119
	EP 746312	B1	20020925		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	JP 09508123	T2	19970819	JP 1995-519690	19950119
	AT 224707	E	20021015	AT 1995-910110	19950119
PRAI	US 1994-184540	A	19940121		
	US 1994-315170	A	19940929		
	WO 1995-US828	W	19950119		

OS MARPAT 123:276077
AB Methods and compns. are disclosed which are useful in preventing and ameliorating cachexia, the clin. syndrome of poor nutritional status and bodily wasting associated with cancer and other chronic diseases. More particularly, the invention relates to aromatic guanylhydrazone (more properly termed amidinohydrazone) compns. and their use to inhibit the uptake of arginine by macrophages and/or its conversion to urea. These compns. and methods are also useful in preventing the generation of nitric oxide (NO) by cells, and so to prevent NO-mediated inflammation and other responses in persons in need of same. In another embodiment, the compds. can be used to inhibit arginine uptake in arginine-dependent tumors and infections. N,N'-bis(3,5-diacetylphenyl)decanediaminde tetrakis(amidinohydrazone) tetrahydrochloride (preparation given) inhibited urea production and arginine transport, inhibited inflammation, prevented fatal endotoxic shock, prevented production of cytokines and NO, conferred protection from focal cerebral infarction, and had antitumor activity.

=> file reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	157.80	212.64

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DICTIONARY FILE UPDATES: 24 NOV 2005 HIGHEST RN 868731-40-2

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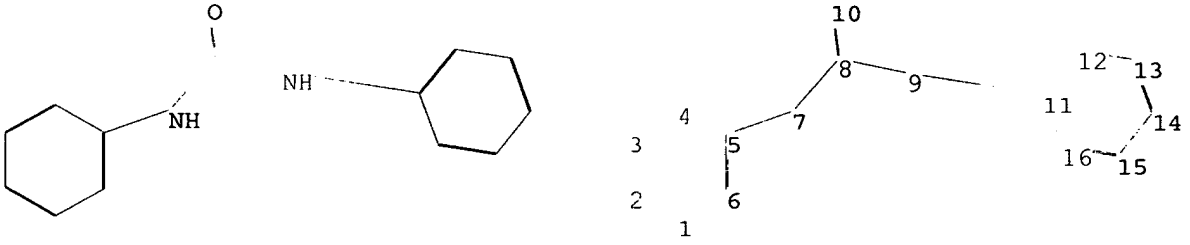

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 35.0% PROCESSED     2000 ITERATIONS                                  50 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:       109728 TO   118792
PROJECTED ANSWERS:           35597 TO    40841

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FULL SEARCH INITIATED 18:11:19 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -   114759 TO ITERATE

100.0% PROCESSED   114759 ITERATIONS                           39177 ANSWERS
SEARCH TIME: 00.00.02

L20       39177 SEA SSS FUL L18

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FULL ESTIMATED COST                                     163.91     376.55

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CA SUBSCRIBER PRICE                                       0.00     -24.09

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FULL ESTIMATED COST	0.45	377.00

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CA SUBSCRIBER PRICE	0.00	-24.09

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FILE LAST UPDATED: 24 Nov 2005 (20051124/ED)

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         63471 HIV
         87554 "MAP"
         13262 "MAPK"
         87554 "MAP"
        252214 "KINASE"
         16089 "MAP KINASE"
                 ("MAP"(W)"KINASE")
L21         67 L20 (L) (HIV OR ("MAP" OR "MAPK" OR "MAP KINASE"))
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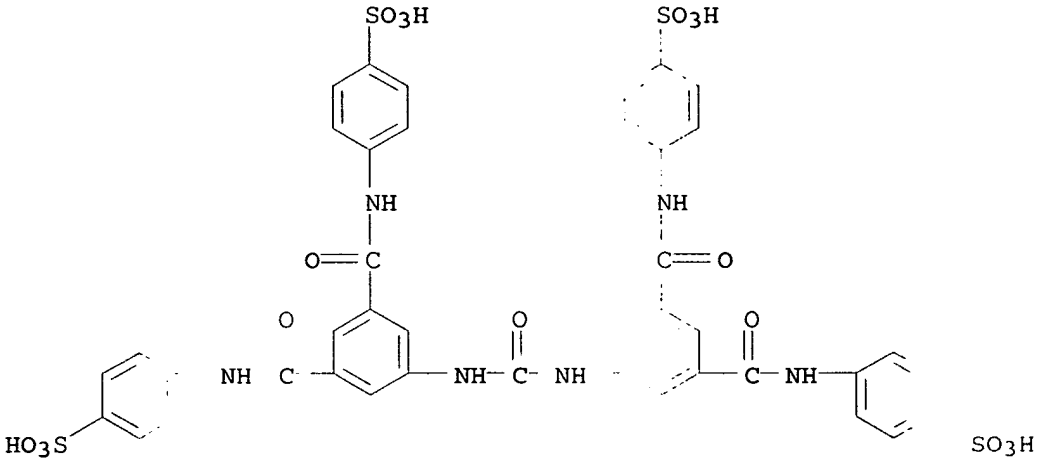
L21 ANSWER 60 OF 67 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1992:439783 CAPLUS
DN 117:39783
TI Naphthalenesulfonic acid derivatives as potential anti-HIV-1 agents. Chemistry, biology and molecular modeling of their inhibition of reverse transcriptase
AU Mohan, P.; Hopfinger, A. J.; Baba, M.
CS Coll. Pharm., Univ. Illinois, Chicago, IL, 60680, USA
SO Antiviral Chemistry & Chemotherapy (1991), 2(4), 215-22
CODEN: ACCHEH; ISSN: 0956-3202
DT Journal
LA English
AB Activity against human immunodeficiency virus (HIV) in the naphthalenesulfonic acid series is most pronounced in the disulfonic acid series. In this class of compds., N-acyl derivs. of 4-amino-5-hydroxy-2,7-naphthalenedisulfonic acid demonstrate significant anti-HIV activity at non-toxic doses. The most potent compds. in this group of agents are bis

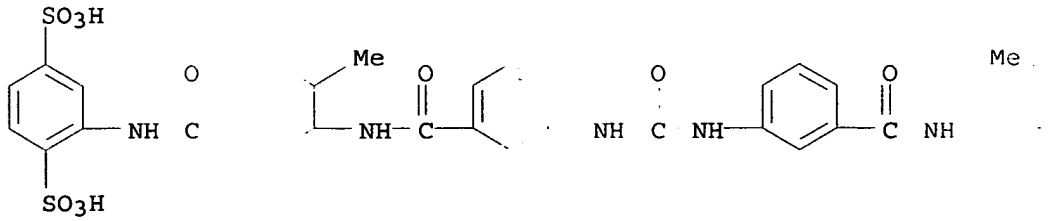
naphthalenedisulfonic acids. A bis derivative containing a decamethylene spacer
demonstrated activity against HIV-1, HIV-2 giant cell formation and reverse transcriptase (RT). This compound was demonstrated and in vitro therapeutic index (ratio of 50%) cytotoxic concentration to 50% inhibitory antiviral concentration) of 10.6. Mol. modeling analyses of this agent, suramin,
and several suramin analogs were undertaken to explain the potent anti-HIV-1 RT activity. These studies are carried out using the mol. decomposition/recompn. strategy, conformational searching, energy minimization and mol. dynamics (MD) simulation. The bis naphthalenedisulfonic acid derivative compound 1, having a flexible decamethylene spacer, was shown to be able to mimic the helical twist of the B-DNA backbone as a low energy conformer state.

IT **138967-72-3 138967-73-4**
RL: BIOL (Biological study)
(conformational anal. of, anti-**HIV**-1 reverse transcriptase activity in relation to)

RN 138967-72-3 CAPLUS
CN Benzenesulfonic acid, 4,4',4'',4'''-[carbonylbis[imino-5,1,3-benzenetriylbis(carbonylimino)]]tetrakis- (9CI) (CA INDEX NAME)



RN 138967-73-4 CAPLUS
CN 1,4-Benzenedisulfonic acid, 2,2'-[carbonylbis[imino-3,1-phenylenecarbonylimino(4-methyl-3,1-phenylene)carbonylimino]]bis- (9CI) (CA INDEX NAME)



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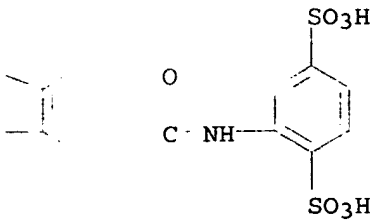
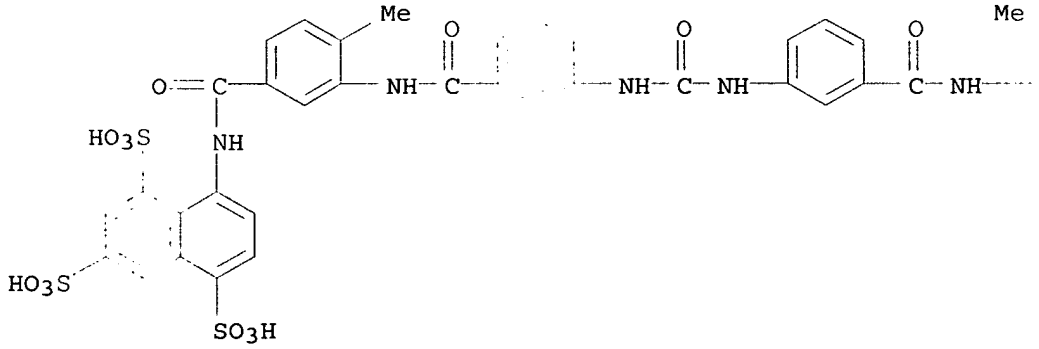


IT **145-63-1**, Suramin
RL: BIOL (Biological study)
(reverse transcriptase of **HIV**-1 inhibition by, mol. modeling anal. of)
RN 145-63-1 CAPLUS
CN 1,3,5-Naphthalenetrisulfonic acid, 8,8'-[carbonylbis[imino-3,1-phenylenecarbonylimino(4-methyl-3,1-phenylene)carbonylimino]]bis- (9CI) (CA INDEX NAME)

PAGE 1-A



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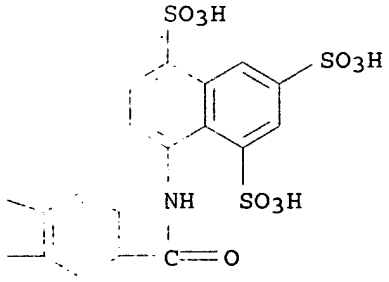
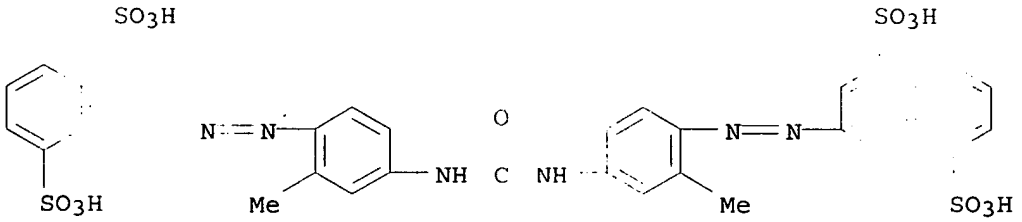


L21 ANSWER 61 OF 67 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1992:227721 CAPLUS
DN 116:227721

TI Inhibition of gp120 binding to the CD4 antigen by dyes: mechanism of effect and contribution to anti-HIV activity
AU Kozlowski, M. R.; Watson, A.
CS Dep. Screening Biochem. Res., Bristol-Myers Squibb Pharm. Res. Inst., Wallingford, CT, 06492-7660, USA
SO Antiviral Chemistry & Chemotherapy (1992), 3(1), 49-53
CODEN: ACCHEH; ISSN: 0956-3202
DT Journal
LA English
AB Several compds. developed for use as dyes have shown activity against HIV-1. The present study examines one putative mechanism of this anti-HIV activity, inhibition of gp120/CD4 binding, and its contribution to the antiviral effects of three chemical classes of dyes. Although, for most dyes, the ability to inhibit gp120/CD4 binding and the reported anti-HIV activities do not correlate, a group of dyes is identified whose anti-HIV activity does appear to be related to binding inhibition. Qual. examination of the effect of two of these dyes on the gp120/CD4 binding isotherm suggests that the inhibition is non-competitive. Dyes which act by preventing viral binding may represent prototypes for the development of novel drugs for the treatment or prevention of AIDS.
IT **3214-47-9**, Direct yellow 50
RL: BIOL (Biological study)
(**HIV**-1 inhibition by, gp120 glycoprotein binding to CD4 antigen in relation to)
RN 3214-47-9 CAPLUS
CN 1,5-Naphthalenedisulfonic acid, 3,3'-[carbonylbis[imino(2-methyl-4,1-phenylene)azo]]bis-, tetrasodium salt (9CI) (CA INDEX NAME)



L21 ANSWER 62 OF 67 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1992:207390 CAPLUS
DN 116:207390
TI Differential activity of polyanionic compounds and castanospermine against HIV replication and HIV-induced syncytium formation depending on virus strain and cell type
AU Schols, D.; Pauwels, R.; Witvrouw, M.; Desmyter, J.; De Clercq, E.
CS Rega Inst. Med. Res., Kathol. Univ. Leuven, Louvain, B-3000, Belg.
SO Antiviral Chemistry & Chemotherapy (1992), 3(1), 23-9
CODEN: ACCHEH; ISSN: 0956-3202
DT Journal
LA English
AB Polyanionic compds. [i.e. pentosan polysulfate, dextran sulfate, heparin, suramin, and aurintricarboxylic acid (ATA)] and castanospermine were examined for their inhibitor effect on human immunodeficiency virus (HIV) strains (HIV-1IIIB, HIV-1RF, HIV-2ROD and HIV-2EHO) in two different assays (HIV cytopathicity in MT-4 cells and HIV antigen expression in CEM cells). In the MT-4 assay dextran sulfate and pentosan polysulfate were more active against HIV-2ROD, suramin was more active against HIV-1RF, and ATA more active against HIV-2EHO-Heparin was less, but castanospermine was more, active against the two HIV-2 strains. In the CEM assay dextran

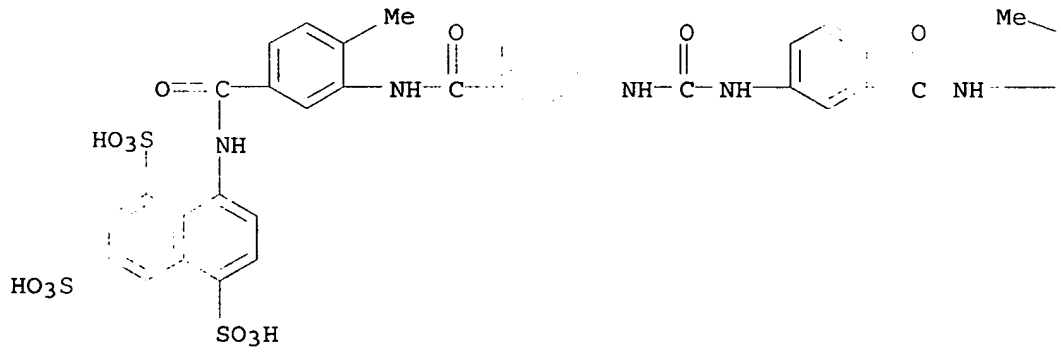
sulfate and suramin were equally active against all HIV strains, pentosan polysulfate was more active against both HIV-2 strains, whereas heparin was less active against HIV-2ROD and ATA again was more active against HIV-2EHO. The compds. and soluble CD4 (sCD4) were also tested in the HIV-induced syncytium formation assay, where chronically infected HUT-78 cells were mixed with uninfected MOLT-4 or CEM cells. The inhibitory effect of suramin and ATA on syncytium formation was independent of the virus strain or cell type. For dextran sulfate and pentosan polysulfate, it was dependent on virus strain, and for heparin, castanospermine, and sCD4, it was dependent on both the virus strain and cell type.

IT **145-63-1**, Suramin
RL: BIOL (Biological study)
(**HIV**-1 and **HIV**-2 inhibition by)

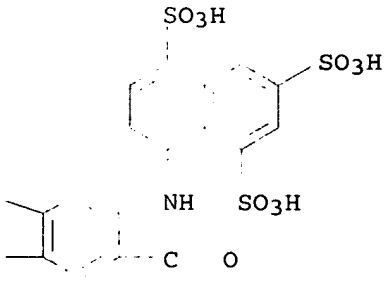
RN 145-63-1 CAPLUS

CN 1,3,5-Naphthalenetrisulfonic acid, 8,8'-[carbonylbis[imino-3,1-phenylenecarbonylimino(4-methyl-3,1-phenylene)carbonylimino]]bis- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B



L21 ANSWER 63 OF 67 CAPLUS COPYRIGHT 2005 ACS on STN

AN 1992:34553 CAPLUS

DN 116:34553

TI Antiviral compositions containing azo dye derivatives and methods for using them

IN Aszalos, Adorjan; Weaver, James L.; Pine, Scott

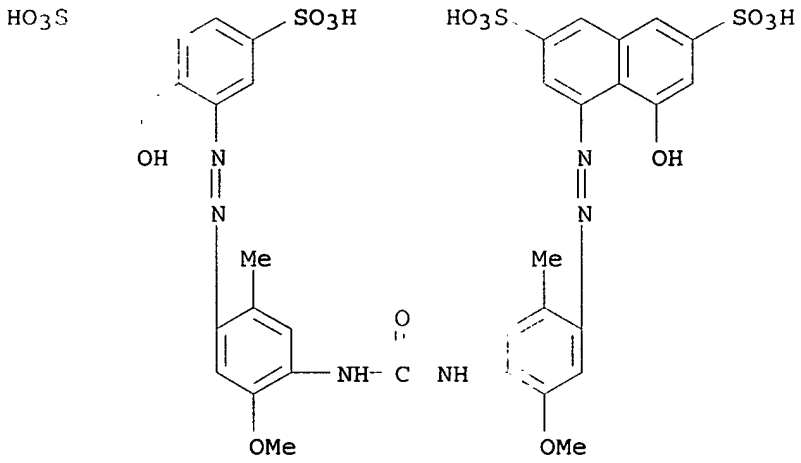
PA United States Food and Drug Administration, USA
SO U. S. Pat. Appl., 23 pp. Avail. NTIS Order No. PAT-APPL-6-684 258.
CODEN: XAXXAV
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 684258	A0	19910801	US 1991-684258	19910412
	US 5650441	A	19970722	US 1994-320852	19941011
PRAI	US 1991-684258	B1	19910412		
	US 1992-978144	B3	19921116		

AB Azo dyes are able to block the binding of HIV to its cellular receptor CD4, and thus exhibit antiviral activity. C.I. direct red 79 inhibited the production of reverse transcriptase activity in human peripheral blood lymphocyte after 6 days of culture by 97% at 100 mM concentration

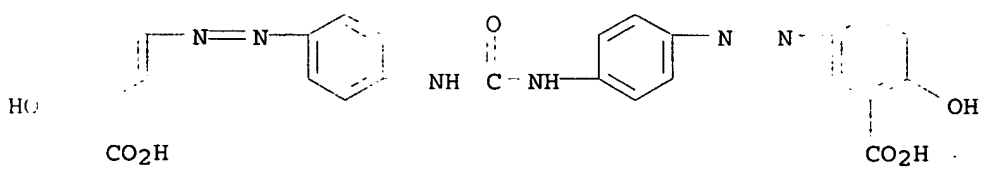
IT **1937-34-4**, C.I. Direct red 79 **2829-42-7**, C.I. Direct yellow 26 **2829-43-8**, C.I. Direct red 75 **3214-47-9**, C.I. Direct yellow 50
RL: BIOL (Biological study)
(virucide against **HIV**)

RN 1937-34-4 CAPLUS
CN 2,7-Naphthalenedisulfonic acid, 4,4'-[carbonylbis[imino(5-methoxy-2-methyl-4,1-phenylene)azo]]bis[5-hydroxy-, tetrasodium salt (9CI) (CA INDEX NAME)



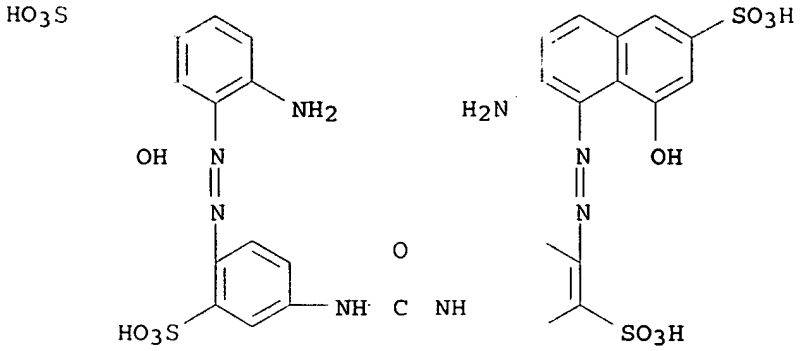
●4 Na

RN 2829-42-7 CAPLUS
CN Benzoic acid, 3,3'-[carbonylbis(imino-4,1-phenyleneazo)]bis[6-hydroxy-, disodium salt (9CI) (CA INDEX NAME)



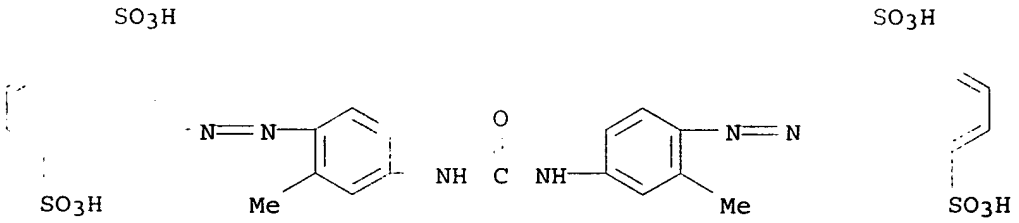
●2 Na

RN 2829-43-8 CAPLUS
CN 2-Naphthalenesulfonic acid, 5,5'-[carbonylbis[imino(2-sulfo-4,1-phenylene)azo]]bis[6-amino-4-hydroxy-, tetrasodium salt (9CI) (CA INDEX NAME)



●4 Na

RN 3214-47-9 CAPLUS
CN 1,5-Naphthalenedisulfonic acid, 3,3'-[carbonylbis[imino(2-methyl-4,1-phenylene)azo]]bis-, tetrasodium salt (9CI) (CA INDEX NAME)



●4 Na

L21 ANSWER 64 OF 67 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1990:612013 CAPLUS
DN 113:212013
TI Preparation of phenanthrolinedicarboxylate esters, 4-aminoquinoline and isoquinoline derivatives as inhibitors of HIV reverse transcriptase
IN Althaus, Irene W.; Reusser, Fritz; Tarpley, William Gary; Skaletzky, Louis L.
PA Upjohn Co., USA
SO PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9005523	A2	19900531	WO 1989-US4774	19891030
	WO 9005523	A3	19900712		
	W: AU, DK, FI, HU, JP, KR, NO, SU, US				
	RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
	AU 8944889	A1	19900612	AU 1989-44889	19891030

PRAI US 1988-271567 A 19881115
US 1988-279364 A 19881202
US 1988-287448 A2 19881220
WO 1989-US4774 A 19891030
OS MARPAT 113:212013
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

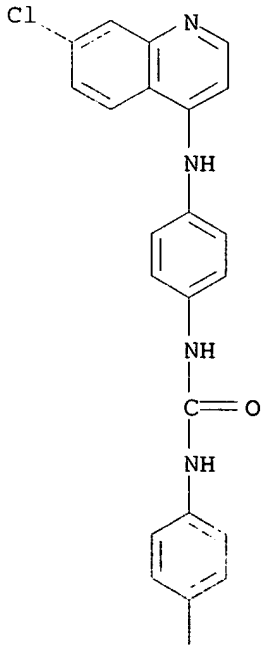
AB The title compds. [I, II, III, IV, etc.; R = C1-8 alkyl, C5-8 cycloalkly, Ph; R1, R2 = CO2H-protecting ester group; R3 = N-benzoyl- or N-phenylsulfonylpiperazin-4-ylcarbonyl, NHCONHPh, or N-(4-phenylcyclohex-3-en-1-yl)carbamoyl optionally substituted on the Ph ring, morpholinocarbonyl; R4 = F, Cl, Br, CF3; X = H, F Cl, Br, CF3, C1-3 alkoxy; R5 = H, Ph or PhCH2 optionally substituted on the Ph ring; R6, R7 = H, C1-3 alkoxy or alkoxycarbonylmethyl] some of which are new, known, or com. available, are useful for treatment of patients afflicted with HIV. Thus, to 1-[4-[(7-trifluoromethyl-4-quinolinyl)amino]benzoyl]piperazine in the THF was added Et3N followed by BzCl and the resulting mixture was stirred 24 h at room temperature to give 1-benzoyl-4-[4-[(7-trifluoromethyl-4-quinolinyl)amino]benzoyl]piperazine. A total of 16 I were prepared and 6,7-dimethoxy-1-(3,4,5-triethoxyphenyl)isoquinoline HCl (octaverine HCl) (V) inhibited 70% at 2.30 μM HIV-induced syncytia formation in a tissue culture of MT-2 cells. Tablets containing V and 8 other pharmaceutical compns. containing 7 specific I were formulated.

IT **130292-77-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as **HIV** reverse transcriptase inhibitor)

RN 130292-77-2 CAPLUS

CN Urea, N-(4-chlorophenyl)-N'-[4-[(7-chloro-4-quinolinyl)amino]phenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



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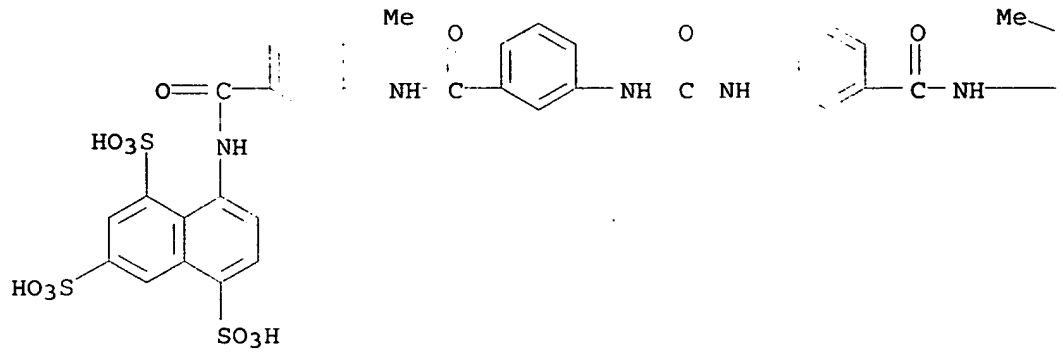
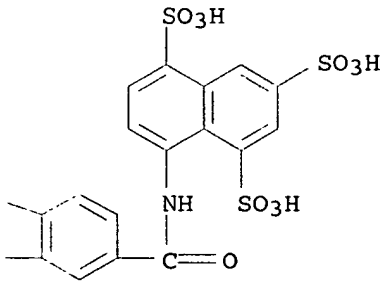
L21 ANSWER 65 OF 67 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1990:526079 CAPLUS
DN 113:126079
TI Sulfated polysaccharides as potent inhibitors of HIV-induced syncytium formation: a new strategy towards AIDS chemotherapy
AU Baba, Masanori; Schols, Dominique; Pauwels, Rudi; Nakashima, Hideki; De Clercq, Erik
CS Rega Inst. Med. Res., Univ. Leuven, Louvain, B-3000, Belg.
SO Journal of Acquired Immune Deficiency Syndromes (1990), 3(5), 493-9
CODEN: JAISET; ISSN: 0894-9255
DT Journal
LA English
AB Multinucleated giant cell (syncytium) formation induced by the interaction between the gp120 glycoprotein expressed on the surface of cells infected with human immunodeficiency virus type 1 (HIV-1) and the CD4 receptor of uninfected CD4-pos. (CD4+) cells may play an important role in the depletion of T4 lymphocytes in acquired immune deficiency syndrome (AIDS) patients. Using a double fluorescence cell-staining technique and anal. of the cells by the fluorescence-activated cell sorter (FACS), it was demonstrated that giant cell formation between persistently HIV-1-infected HUT-78 cells and uninfected MOLT-4 cells results in a selective destruction of the uninfected CD4+ MOLT-4 cells. Apparently, bystander CD4+ cells may serve as targets for the killing effect of the HIV-1-infected cells, and this killing effect is preceded by fusion between the target (uninfected) and aggressor (infected) cells. Pentosan polysulfate, dextran sulfate, and various other sulfated polysaccharides, but not heparin, have proved to inhibit this cell fusion process and hence protect the target CD4+ cells against destruction by the killer HIV-1-infected cells. Azidothymidine does not interfere with this process. Assuming that fusion between HIV-infected and uninfected CD4+ cells is a crucial event in the pathogenesis of AIDS, any compds. that specifically interfere with this process may be therapeutically advantageous in the treatment of this disease.
IT **145-63-1**, Suramin
RL: BIOL (Biological study)
(**HIV**-induced syncytium formation by T-lymphocytes response to)
RN 145-63-1 CAPLUS
CN 1,3,5-Naphthalenetrisulfonic acid, 8,8'-[carbonylbis[imino-3,1-phenylenecarbonylimino(4-methyl-3,1-phenylene)carbonylimino]]bis- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B



L21 ANSWER 66 OF 67 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1990:210583 CAPLUS
DN 112:210583
TI Dextran sulfate and other polyanionic anti-HIV compounds specifically interact with the viral gp120 glycoprotein expressed by T-cells persistently infected with HIV-1
AU Schols, Dominique; Pauwels, Rudi; Desmyter, Jan; De Clercq, Erik
CS Rega Inst. Med. Res., Kathol. Univ. Leuven, Louvain, B-3000, Belg.
SO Virology (1990), 175(2), 556-61
CODEN: VIRLAX; ISSN: 0042-6822
DT Journal
LA English
AB Eighty to 100% of persistently HIV-1-infected HUT-78 cells express the viral glycoprotein gp120 as demonstrated with anti-gp120 monoclonal antibody (mAb) and fluorescence-activated cell sorter anal. Several polyanionic anti-HIV compds., e.g., dextran sulfate, pentosan polysulfate, heparin, aurintricarboxylic acid (ATA), suramin, and Evans blue, which are known to inhibit the adsorption of HIV particles to CD4+ cells, prevented the binding of anti-gp120 mAb to the persistently HIV-1-infected HUT-78 cells. This effect was concentration dependent and reversible. Except for ATA, the polyanionic compds. did not interfere with the binding of Leu3a/OKT4A mAB, indicating that they do not directly bind to the CD4 receptor. Thus, the inhibitory effect of dextran sulfate and its congeners on the

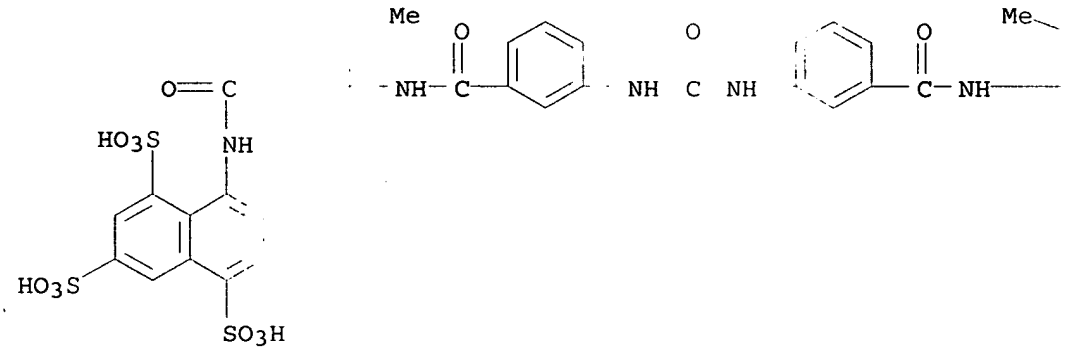
interaction of the HIV gp120 with the cellular CD4 receptor can be ascribed to a specific binding of gp120.

IT **145-63-1**, Suramin
RL: PROC (Process)
(binding of, to **HIV**-1 glycoprotein gp120)

RN 145-63-1 CAPLUS

CN 1,3,5-Naphthalenetrisulfonic acid, 8,8'-[carbonylbis[imino-3,1-phenylenecarbonylimino(4-methyl-3,1-phenylene)carbonylimino]]bis- (9CI) (CA INDEX NAME)

PAGE 1-A



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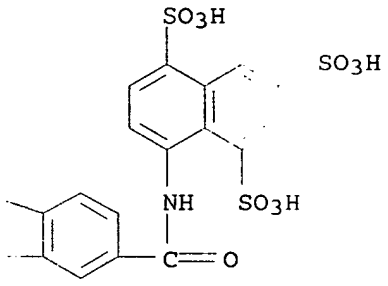


L21 ANSWER 67 OF 67 CAPLUS COPYRIGHT 2005 ACS on STN

AN 1990:91265 CAPLUS

DN 112:91265

TI Inhibition of human immunodeficiency virus type 1 RNase H by sulfated polyanions

AU Moelling, Karin; Schulze, Thomas; Diringer, Heino

CS Abt. Schuster, Max-Planck-Inst. Mol. Genet., Berlin, D-1000/33, Fed. Rep. Ger.

SO Journal of Virology (1989), 63(12), 5489-91
CODEN: JOVIAM; ISSN: 0022-538X

DT Journal

LA English

AB The effect of sulfated polysaccharides on human immunodeficiency virus type 1 recombinant reverse transcriptase (RT) and RNase H activities was

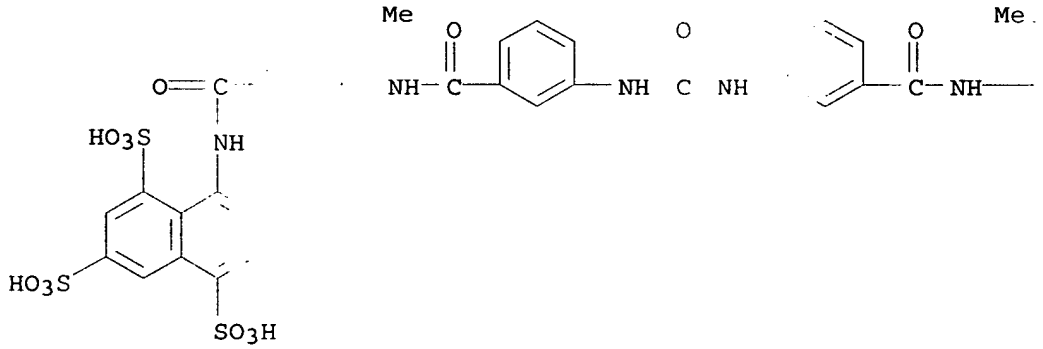
analyzed in vitro. Heparin, dextran sulfates, and xylan polysulfate were much more potent inhibitors of RNase H than of RT and exhibited 50% inhibitory concns. of 0.04 to 0.1 μg/mL (corresponding to 0.1-25 nM) which is up to 5000-fold more efficient than that against RT. Inhibitors of RNase H activity are attractive as antiviral drugs.

IT **145-63-1**, Suramin
RL: BIOL (Biological study)
(reverse transcriptase and RNase H of **HIV** inhibition by)

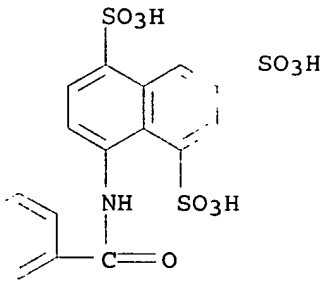
RN 145-63-1 CAPLUS

CN 1,3,5-Naphthalenetrisulfonic acid, 8,8'-[carbonylbis[imino-3,1-phenylenecarbonylimino(4-methyl-3,1-phenylene)carbonylimino]]bis- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B



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SEL RN

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L2 4 SEA (164301-51-3/BI OR 165245-96-5/BI OR 208197-81-3/BI OR

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L4          7938 SEA L3 AND P38
L5            82 SEA L4 AND HIV
L6          7775 SEA L3 (L) P38
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L8            28 SEA L7 (L) (MAPK OR "MAP KINASE")
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L10        95386 SEA L9 (L) P38 OR ("MAP" OR "MAPK" OR "MAP KINASE")
L11            6 SEA L9 (L) (P38 OR ("MAP" OR "MAPK" OR "MAP KINASE"))
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L13            1 SEA L12 (L) HIV
                D BIB ABS HITSTR
L14           59 SEA 164301-51-3/RN
                D 59 BIB ABS HITSTR
L15           14 SEA L14 AND (HIV OR ("MAP" OR "MAP KINASE" OR "MAPK"))
                D 10-14 BIB ABS HITSTR
L16            9 SEA L14 AND VIRUS
                D 8-9 BIB ABS HITSTR
L17           59 SEA 164301-51-3/RN
                D 50-58 BIB ABS

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L20        39177 SEA SSS FUL L18

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     FILE 'CAPLUS' ENTERED AT 18:11:28 ON 25 NOV 2005
L21           67 SEA L20 (L) (HIV OR ("MAP" OR "MAPK" OR "MAP KINASE"))
                D 60-67 BIB ABS HITSTR


     FILE HOME

     FILE CAPLUS

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DICTIONARY FILE UPDATES: 24 NOV 2005 HIGHEST RN 868731-40-2

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http://www.cas.org/ONLINE/UG/regprops.html

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FULL ESTIMATED COST	52.12	429.12

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CA SUBSCRIBER PRICE	-5.84	-29.93

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PASSWORD:
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NEWS 4	OCT 03	MATHDI removed from STN
NEWS 5	OCT 04	CA/CAplus-Canadian Intellectual Property Office (CIPO) added to core patent offices
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NEWS 10	OCT 27	EPFULL enhanced with additional content
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FILE 'HOME' ENTERED AT 19:23:29 ON 25 NOV 2005

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'CAPLUS' ENTERED AT 19:23:46 ON 25 NOV 2005
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FILE COVERS 1907 - 25 Nov 2005 VOL 143 ISS 23
FILE LAST UPDATED: 24 Nov 2005 (20051124/ED)

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=> s us5599984/pn
L1 3 US5599984/PN

=> sel rn
E1 THROUGH E112 ASSIGNED

=> file reg

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FULL ESTIMATED COST	2.58	2.79

FILE 'REGISTRY' ENTERED AT 19:24:25 ON 25 NOV 2005
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STRUCTURE FILE UPDATES: 24 NOV 2005 HIGHEST RN 868731-40-2
DICTIONARY FILE UPDATES: 24 NOV 2005 HIGHEST RN 868731-40-2

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*                                                                    *
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* the IDE default display format and the ED field has been added,   *
* effective March 20, 2005.  A new display format, IDERL, is now    *
* available and contains the CA role and document type information. *
*                                                                    *
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Structure search iteration limits have been increased. See HELP SLIMITS
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predicted properties as well as tags indicating availability of
experimental property data in the original document. For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

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=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.43	3.22

FILE 'CAPLUS' ENTERED AT 19:24:49 ON 25 NOV 2005

FILE COVERS 1907 - 25 Nov 2005 VOL 143 ISS 23
FILE LAST UPDATED: 24 Nov 2005 (20051124/ED)


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=> s l2
L3      248318 L2

=> s l3 (L) (HIV or p38 or ("MAP" or "MAPK" or "map kinase"))
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         11143 P38
         87554 "MAP"
         13262 "MAPK"
         87554 "MAP"
        252214 "KINASE"
         16089 "MAP KINASE"
                 ("MAP"(W)"KINASE")
L4        569 L3 (L) (HIV OR P38 OR ("MAP" OR "MAPK" OR "MAP KINASE"))

=> s l3 (L) p38
         11143 P38
L5         165 L3 (L) P38

=> d 160-165 bib abs hitstr
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L5 ANSWER 160 OF 165 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:38210 CAPLUS
DN 130:208791
TI Activation of p38 mitogen-activated protein kinase by lipopolysaccharide in human neutrophils requires nitric oxide-dependent cGMP accumulation
AU Browning, Darren D.; Windes, Nancy D.; Ye, Richard D.
CS Department of Immunology, The Scripps Research Institute, La Jolla, CA, 92037, USA
SO Journal of Biological Chemistry (1999), 274(1), 537-542
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB This study examined the signal transduction pathway(s) leading to phosphorylation of p38 in human neutrophils stimulated with lipopolysaccharide and formyl peptides. Blockade of the nitric oxide (NO) pathway in neutrophils with the NO synthase inhibitor N-nitro-L-arginine Me ester or by treatment with the NO scavenger 2-phenyl-tetramethylimidazoline-1-oxyl-3-oxide attenuated phosphorylation of the mitogen-activated protein kinase p38 in response to lipopolysaccharide but not fMet-Leu-Phe. Using the NO releasing agents S-nitroso-N-acetylpenicillamine and sodium nitroprusside it was determined that nitric oxide is sufficient to cause an increase in phosphorylation of p38. Increasing cellular cGMP with phosphodiesterase inhibitors, by stimulation of soluble guanylyl cyclase with YC-1 or with exogenous dibutyryl cGMP resulted in mitogen-activated protein kinase/extracellular signal-regulated kinase kinase 3,6 (MEK3,6) activation and phosphorylation of p38. This phenomenon was specific for MEK3,6, because these agents had no effect on the phosphorylation state of MEK1,2. A role for protein kinase G but not protein kinase A downstream of lipopolysaccharide but not formyl-Met-Leu-Phe was shown using the specific inhibitors KT5823 and H89,

resp. Thus, activation of p38 by fMet-Leu-Phe and lipopolysaccharide involve different mechanisms, and activation of protein kinase G by NO-dependent stimulation of guanylyl cyclase is necessary and sufficient for phosphorylation of p38 downstream of lipopolysaccharide.

IT **10102-43-9**, Nitric oxide, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**p38** mitogen-activated protein kinase activation by lipopolysaccharide in human neutrophils requires nitric oxide-dependent cGMP accumulation)

RN 10102-43-9 CAPLUS
CN Nitrogen oxide (NO) (8CI, 9CI) (CA INDEX NAME)

N O

RE.CNT 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 161 OF 165 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:408507 CAPLUS
DN 129:144658
TI SB 203580 inhibits p38 mitogen-activated protein kinase, nitric oxide production, and inducible nitric oxide synthase in bovine cartilage-derived chondrocytes
AU Badger, Alison M.; Cook, Michael N.; Lark, Michael W.; Newman-Tarr, Tonie M.; Swift, Barbara A.; Nelson, Allen H.; Barone, Frank C.; Kumar, Sanjay
CS Departments of Bone and Cartilage Biology and Cardiovascular Pharmacology, SmithKline Beecham Pharmaceuticals, King of Prussia, PA, 19406, USA
SO Journal of Immunology (1998), 161(1), 467-473
CODEN: JOIMA3; ISSN: 0022-1767
PB American Association of Immunologists
DT Journal
LA English
AB Nitric oxide (NO) is implicated in a number of inflammatory processes and is an important mediator in animal models of rheumatoid arthritis and in in vitro models of cartilage degradation The pyridinyl imidazole SB 203580 inhibits p38 mitogen-activated protein (MAP) kinase in vitro, blocks proinflammatory cytokine production in vitro and in vivo, and is effective in animal models of arthritis. The purpose of this study was to determine whether SB 203580 could inhibit p38 MAP kinase activity, NO production, and inducible NO synthase (iNOS) in IL-1 stimulated bovine articular cartilage/chondrocyte cultures. The results indicated that SB 203580 inhibited both IL-1 stimulated p38 MAP kinase activity in isolated chondrocytes and NO production in bovine chondrocytes and cartilage explants with an IC50 value of approx. 1 μM. To inhibit NO production, SB 203580 had to be present in cartilage explant cultures during the first 8 h of IL-1 stimulation, and activity was lost when it was added 24 h following IL-1. SB 203580 did not inhibit iNOS activity, as measured by the conversion of arginine to citrulline, when added directly to cultures where the enzyme had already been induced, but had to be present during the induction period. Using a 372-bp probe for bovine iNOS we demonstrated inhibition of IL-1-induced mRNA by SB 203580 at both 4 and 24 h following IL-1 treatment. The iNOS mRNA levels were consistent with NO levels in 24-h cell culture supernatants of the IL-1-stimulated bovine chondrocytes used to obtain the RNA.

IT **10102-43-9**, Nitric oxide, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(SB 203580 inhibits **p38** mitogen-activated protein kinase, nitric oxide production, and inducible nitric oxide synthase in bovine cartilage-derived chondrocytes)

RN 10102-43-9 CAPLUS

CN Nitrogen oxide (NO) (8CI, 9CI) (CA INDEX NAME)

N O

RE.CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 162 OF 165 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:403996 CAPLUS
DN 129:135005
TI Interleukin-1β-induced rat pancreatic islet nitric oxide synthesis requires both the p38 and extracellular signal-regulated kinase 1/2 mitogen-activated protein kinases
AU Larsen, Claus M.; Wadt, Karin A. W.; Juhl, Lone F.; Andersen, Henrik U.; Karlsen, Allan E.; Su, Michael S.-S.; Seedorf, Klaus; Shapiro, Leland; Dinarello, Charles A.; Mandrup-Poulsen, Thomas
CS Univ. Colorado Health Sciences Center, Denver, CO, 80262, USA
SO Journal of Biological Chemistry (1998), 273(24), 15294-15300
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB Interleukin-1β (IL-1β) is cytotoxic to rat pancreatic β-cells by inhibiting glucose oxidation, causing DNA damage, and inducing apoptosis. Nitric oxide (NO) is a necessary but not sufficient mediator of these effects. IL-1β induced kinase activity toward Elk-1, activation transcription factor 2, c-Jun, and heat shock protein 25 in rat islets. By Western blotting with phosphospecific antibodies and by immunocomplex kinase assay, IL-1β was shown to activate extracellular signal-regulated kinase (ERK) 1/2 and p38 mitogen-activated protein kinase (p38) in islets and rat insulinoma cells. Specific ERK1/2 and p38 inhibitors individually reduced but in combination blocked IL-1β-mediated islet NO synthesis, and reverse transcription-polymerase chain reaction of inducible NO synthase mRNA showed that ERK1/2 and p38 controlled IL-1β-induced islet inducible NO synthase expression at the transcriptional level. Hyperosmolarity caused phosphorylation of Elk-1, activation of transcription factor 2, and heat shock protein 25, and activation of ERK1/2 and p38 in islets comparable to that induced by IL-1β but did not lead to NO synthesis. Inhibition of p38 but not of ERK1/2 attenuated IL-1β-mediated inhibition of glucose-stimulated insulin release. Thus, ERK1/2 and p38 activation is necessary but not sufficient for IL-1β-mediated β-cell NO synthesis and p38 is involved in signaling of NO-independent effects of IL-1β in β-cells.
IT **10102-43-9**, Nitric oxide, biological studies
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(ERK1/2 and **p38** kinases activation is necessary but not sufficient for interleukin-1β-mediated β-cell nitric oxide formation and **p38** is involved in signaling of NO-independent effects of IL-1β in pancreatic β-cells)
RN 10102-43-9 CAPLUS
CN Nitrogen oxide (NO) (8CI, 9CI) (CA INDEX NAME)

N O

RE.CNT 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 163 OF 165 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:129074 CAPLUS

DN 128:256329
TI Extracellular signal-regulated kinase and p38 subgroups of mitogen-activated protein kinases regulate inducible nitric oxide synthase and tumor necrosis factor-α gene expression in endotoxin-stimulated primary glial cultures
AU Bhat, Narayan R.; Zhang, Peisheng; Lee, John C.; Hogan, Edward L.
CS Department of Neurology, Medical University of South Carolina, Charleston, SC, 29425, USA
SO Journal of Neuroscience (1998), 18(5), 1633-1641
CODEN: JNRSDS; ISSN: 0270-6474
PB Society for Neuroscience
DT Journal
LA English
AB Tumor necrosis factor-α (TNFα) and nitric oxide (NO), the product of inducible NO synthase (iNOS), mediate inflammatory and immune responses in the CNS under a variety of neuropathol. situations. They are produced mainly by "activated" astrocytes and microglia, the two immune regulatory cells of the CNS. Here, the authors examined the regulation of TNFα and iNOS gene expression in endotoxin-stimulated primary glial cultures, focusing on the role of mitogen-activated protein (MAP) kinase cascades. The bacterial lipopolysaccharide (LPS) was able to activate extracellular signal-regulated kinase (ERK) and p38 kinase subgroups of MAP kinases in microglia and astrocytes. ERK activation was sensitive to PD98059, the kinase inhibitor that is specific for ERK kinase. The activity of p38 kinase was inhibited by SB203580, a member of the novel class of cytokine suppressive anti-inflammatory drugs (CSAIDs), as revealed by blocked activation of the down-stream kinase, MAP kinase-activated protein kinase-2. The treatment of glial cells with either LPS alone (microglia) or a combination of LPS and interferon-γ (astrocytes) resulted in an induced production of NO and TNFα. The two kinase inhibitors, at micromolar concns., individually suppressed and, in combination, almost completely blocked glial production of NO and the expression of iNOS and TNFα, as determined by Western blot anal. Reverse transcriptase-PCR anal. showed changes in iNOS mRNA levels that paralleled iNOS protein and NO while indicating a lack of effect of either of the kinase inhibitors on TNFα mRNA expression. The results demonstrate key roles for ERK and p38 MAP kinase cascades in the transcriptional and post-transcriptional regulation of iNOS and TNFα gene expression in endotoxin-activated glial cells.
IT **10102-43-9**, Nitric oxide, biological studies
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(ERK kinase and **p38** MAP kinase regulate inducible nitric oxide synthase and tumor necrosis factor-α gene expression in endotoxin-stimulated neuroglial cells)
RN 10102-43-9 CAPLUS
CN Nitrogen oxide (NO) (8CI, 9CI) (CA INDEX NAME)

N O

RE.CNT 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 164 OF 165 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1997:734919 CAPLUS
DN 128:59787
TI Blockade of p38 mitogen-activated protein kinase pathway inhibits inducible nitric-oxide synthase expression in mouse astrocytes
AU Da Silva, Jean; Pierrat, Benoit; Mary, Jean-Luc; Lesslauer, Werner
CS Dep. Cent. Nervous System diseases, PRPN, F. Hoffmann-La Roche, Ltd., Basel, 4070, Switz.
SO Journal of Biological Chemistry (1997), 272(45), 28373-28380
CODEN: JBCHA3; ISSN: 0021-9258

PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB Treatment of mouse astrocyte cultures with combined interleukin (IL)-1α and tumor necrosis factor (TNF)-α induced expression of inducible nitric-oxide synthase (iNOS), resulting in sustained release of large amts. of nitric oxide, whereas TNF-α and IL-1α individually were unable to induce iNOS expression in astrocytes. The role of MAPK cascades and of NF-κB activation in the early intracellular signal transduction involved in iNOS transcription in TNF-α/IL-1α-stimulated astrocytes was investigated. TNF-α and IL-1α activated all p42/44MAPK, p38MAPK, AND P54JNK pathways as determined by immunopptn. kinase assays using specific antibodies and substrates. The p38MAPK pathway is specifically involved in TNF-α/IL-1α-induced iNOS expression, since iNOS protein and nitric oxide release in the presence of a specific inhibitor of p38MAPK, 4-(4-fluorophenyl)-2-2-(4-hydroxyphenyl)-5-(4-pyridyl)-imidazole (FHPI), were dramatically diminished. In contrast, PD98059, a specific inhibitor of MEK1 had no effect on iNOS expression. P38MAPK did not couple NF-κB to iNOS transcription, but NF-κB had a clear role in iNOS transcription regulation. Northern blot anal. showed that the p38MAPK pathway controlled iNOS expression at the transcriptional level, since iNOS mRNA was reduced in the presence of FHPI in TNF-α/IL-1α-stimulated astrocytes. INOS expression was investigated with TNF receptor (TNFR)-1- and TNFR-2-deficient mice. The TNF-α activity in TNF-α-stimulated astrocytes was exclusively mediated through TNFR-1, most likely because TNFR-2-mediated signals in astrocytes dd not connect to the p38MAPK pathway. These data suggest that TNF-α/IL-1α-induced iNOS expression depends on a yet undetd. second pathway in addition to p38MAPK.
IT **10102-43-9**, Nitric oxide, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(release; blockade of **p38** mitogen-activated protein kinase pathway inhibits inducible nitric-oxide synthase expression in mouse astrocytes)
RN 10102-43-9 CAPLUS
CN Nitrogen oxide (NO) (8CI, 9CI) (CA INDEX NAME)

N═O

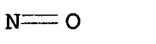
RE.CNT 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 165 OF 165 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1997:211817 CAPLUS
DN 126:276157
TI p38 mitogen-activated protein kinase down-regulates nitric oxide and up-regulates prostaglandin E2 biosynthesis stimulated by interleukin-1β
AU Guan, Zhonghong; Baier, Lisa D.; Morrison, Aubrey R.
CS Department Molecular Biology Pharmacology Medicine, Washington University School Medicine, St. Louis, MO, 63110, USA
SO Journal of Biological Chemistry (1997), 272(12), 8083-8089
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB The inflammatory cytokine interleukin 1β (IL-1β) induces both cyclooxygenase-2 (Cox-2) and the inducible nitric-oxide synthase (iNOS) with increases in the release of prostaglandins (PGs) and nitric oxide (NO) from glomerular mesangial cells. However, the intracellular signaling mechanisms by which IL-1β induces iNOS and Cox2 expression

is obscure. Our current studies demonstrate that IL-1β produces a rapid increase in p38 mitogen-activated protein kinase (MAPK) phosphorylation and activation. Serum starvation and SC68376, a drug which selectively inhibits p38 MAPK in mesangial cells, were used to investigate whether p38 MAPK contributes to the signaling mechanism of IL-1β induction of NO and PG synthesis. Serum starvation and SC68376 selectively inhibited IL-1β-induced activation of p38 MAPK. Both SC68376 and serum starvation enhanced NO biosynthesis by increasing iNOS mRNA expression, protein expression, and nitrite production In contrast, both SC68376 and serum starvation suppressed PG release by inhibiting Cox2 mRNA, protein expression, and PGE2 synthesis. These data demonstrate that IL-1β phosphorylates and activates p38 MAPK in mesangial cells. The activation of p38 MAPK may provide a crucial signaling mechanism, which mediates the up-regulation of PG synthesis and the down-regulation of NO biosynthesis induced by IL-1β.

IT **10102-43-9**, Nitric oxide, biological studies
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(**p38** mitogen-activated protein kinase down-regulates nitric oxide and up-regulates PGE2 biosynthesis stimulated by interleukin-1β)

RN 10102-43-9 CAPLUS
CN Nitrogen oxide (NO) (8CI, 9CI) (CA INDEX NAME)



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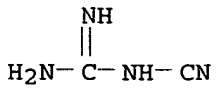
=> s l4
         63471 HIV
         11143 P38
         87554 "MAP"
         13262 "MAPK"
         87554 "MAP"
        252214 "KINASE"
         16089 "MAP KINASE"
                 ("MAP"(W)"KINASE")
L6         569 L3 (L) (HIV OR P38 OR ("MAP" OR "MAPK" OR "MAP KINASE"))

=> d 569 bib abs hitstr

L6   ANSWER 569 OF 569  CAPLUS  COPYRIGHT 2005 ACS on STN
AN   1979:474100  CAPLUS
DN   91:74100
TI   Electron density maps of bent bonds in noncyclic molecules
AU   Eisenstein, M.; Hirshfeld, F. L.
CS   Dep. Struct. Chem., Weizmann Inst. Sci., Rehovot, Israel
SO   Chemical Physics (1979), 38(1), 1-10
     CODEN: CMPHC2; ISSN: 0301-0104
DT   Journal
LA   English
AB   Electron-d. maps, derived exptl. (x-ray diffraction) or theor.
     (extended-basis SCF calcns.), show that bond bending due to unbalanced
     1,3-steric repulsions is expressed in a deformation-d. peak slightly
     displaced off the bond axis. This is demonstrated in (NH2)2C:NCN, HN3,
     N3CN, HCO2H, and HN:NH. Besides accounting for tilted Me groups, as in
     MeOH, and numerous similar violations of local symmetry, the
     flexible-spring model rationalizes a variety of conformational effects,
     such as the preferred syn-planar conformation of carboxylic acids, where
     the axis of internal rotation does not coincide with the internuclear
     vector.
IT   461-58-5
     RL: PRP (Properties)
```

(electron d. **map** of, bent-flexible-spring model for bent bonds and)
RN 461-58-5 CAPLUS
CN Guanidine, cyano- (8CI, 9CI) (CA INDEX NAME)



=> s l4 and guanylhydrazone
1141 GUANYLHYDRAZONE
L7 2 L4 AND GUANYLHYDRAZONE

=> d 1-2 bib abs

L7 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:62440 CAPLUS
DN 136:256901
TI Inhibition of stress-activated MAP kinases induces clinical improvement in moderate to severe Crohn's disease
AU Hommes, Daan; Van Den Blink, Bernt; Plasse, Terry; Bartelsman, Joep; Xu, Cuiping; Macpherson, Bret; Tytgat, Guido; Peppelenbosch, Maikel; Van Deventer, Sander
CS Department of Gastroenterology and Hepatology, University of Amsterdam, Amsterdam, Neth.
SO Gastroenterology (2002), 122(1), 7-14
CODEN: GASTAB; ISSN: 0016-5085
PB W. B. Saunders Co.
DT Journal
LA English
AB Background & Aims: We investigated if inhibition of mitogen-activated protein kinases (MAPKs) was beneficial in Crohn's disease. Methods: Inhibition of JNK and p38 MAPK activation with CNI-1493, a **guanylhydrazone**, was tested in vitro. Twelve patients with severe Crohn's disease (mean baseline, CDAI 380) were randomly assigned to receive either 8 or 25 mg/m2 CNI-1493 daily for 12 days. Clin. endpoints included safety, Crohn's Disease Activity Index (CDAI), Inflammatory Bowel Disease Questionnaire, and the Crohn's Disease Endoscopic Index of Severity. Results: Colonic biopsies displayed enhanced JNK and p38 MAPK activation. CNI-1493 inhibition of both JNK and p38 phosphorylation was observed in vitro. Treatment resulted in diminished JNK phosphorylation and tumor necrosis factor production as well as significant clin. benefit and rapid endoscopic ulcer healing. No serious adverse events were noted. A CDAI decrease of 120 at week 4 (P = 0.005) and 146.5 at week 8 (P = 0.005) was observed A clin. response was seen in 67% of patients at 4 wk and 58% at 8 wk. Clin. remission was observed in 25% of patients at week 4 and 42% at week 8. Endoscopic improvement occurred in all but 1 patient. Response was seen in 3 of 6 infliximab failures, 2 of whom showed remission. Fistulae healing occurred in 4 of 5 patients, and steroids were tapered in 89% of patients. Conclusions: Inflammatory MAPKs are critically involved in the pathogenesis of Crohn's disease and their inhibition provides a novel therapeutic strategy.
RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:119759 CAPLUS
DN 135:121136
TI CNI-1493 prevents induction of endotoxin tolerance by LPS pretreatment in RAW264.7 macrophages
AU Clair, Laurel; Heagy, Wyrta; Tracey, Kevin J.; Rodriguez, Jorge L.; West,

Michael A.
CS Department of Surgery, University of Minnesota, Minneapolis, MN, USA
SO Surgical Forum (2000), 51, 223-225
CODEN: SUFOAX; ISSN: 0071-8041
PB American College of Surgeons
DT Journal
LA English
AB CNI-1493 is a tetravalent **guanylhydrazone** compound that blocks macrophage activation. A study was conducted to determine whether CNI-1493 could block development of endotoxin (LPS) tolerance. Results showed that macrophage inhibitor CNI-1493 prevented development of endotoxin tolerance. Although administration of CNI-1493 to naive macrophages prevented LPS-stimulated tumor necrosis factor (TNF) secretion, CNI-1493 before LPS pretreatment restored LPS-stimulated TNF secretion. It is hypothesized that CNI-1493 blocks the signal transduction pathway through which LPS pretreatment induces endotoxin tolerance. Since CNI-1493 has been shown to interfere with p38 kinase activation, this step may be important in development of endotoxin tolerance. Thus, CNI-1493 may be a useful probe to understand the mechanisms of endotoxin tolerance and could be useful to prevent macrophage dysfunction in sepsis.
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s l4 (L) "map kinase"
87554 "MAP"
252214 "KINASE"
16089 "MAP KINASE"
("MAP"(W)"KINASE")
L8 105 L4 (L) "MAP KINASE"

=> d 100-105 bib abs

L8 ANSWER 100 OF 105 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:154097 CAPLUS
DN 130:292069
TI Activation of the mitogen-activated protein kinase cascade is necessary but not sufficient for basic fibroblast growth factor- and epidermal growth factor-stimulated expression of endothelial nitric oxide synthase in ovine fetoplacental artery endothelial cells
AU Zheng, Jing; Bird, Ian M.; Melsaether, Amy N.; Magness, Ronald R.
CS Department of Obstetrics and Gynecology, Perinatal Research Laboratories, University of Wisconsin, Madison, WI, 53715, USA
SO Endocrinology (1999), 140(3), 1399-1407
CODEN: ENDOAO; ISSN: 0013-7227
PB Endocrine Society
DT Journal
LA English
AB Basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), and vascular endothelial growth factor (VEGF) may play important roles in the placental vasculature, not only by controlling cell growth and differentiation, but also by mediating production of local vasodilators such as nitric oxide. As the mitogen-activated protein kinase (MAPK) signal cascade has been widely associated with cell growth in response to growth factors, herein we investigate whether bFGF, EGF, and VEGF also stimulate expression of endothelial nitric oxide synthase (eNOS) via activation of the MAPK cascade in ovine fetoplacental artery endothelial cells. The presence of the receptors for all three growth factors was confirmed by both immunocytochem. and a functional cell proliferation assay. All three growth factors at 10 ng/mL rapidly (<10 min) activated MAPK. This activation was inhibited by PD 98059, a specific MAPK kinase inhibitor, bFGF and EGF, but not VEGF, dose- and time-dependently increased eNOS protein levels. Maximal stimulatory effects of bFGF and EGF on eNOS protein expression were observed at 10 ng/mL for 24 h of treatment and were associated with elevated eNOS mRNA. PD 98059 also significantly inhibited

bFGF- and EGF-induced increases in eNOS protein expression. Because treatment with all three growth factors resulted in activation of the MAPK cascade, while bFGF and EGF, but not VEGF, increased eNOS expression, we conclude that activation of the MAPK cascade is necessary, but not sufficient, for bFGF- and EGF-induced increases in eNOS protein expression in ovine fetoplacental artery endothelial cells. Thus, addnl. signaling pathways are implicated in the different controls of eNOS expression and mitogenesis by growth factors.

RE.CNT 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 101 OF 105 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:125320 CAPLUS
DN 130:336721
TI Interleukin-1β regulation of inducible nitric oxide synthase and cyclooxygenase-2 involves the p42/44 and p38 MAPK signaling pathways in cardiac myocytes
AU LaPointe, Margot C.; Isenovic, Esma
CS Hypertension and Vascular Research Division, Henry Ford Hospital, Detroit, MI, USA
SO Hypertension (1999), 33(1, Pt. 2), 276-282
CODEN: HPRTDN; ISSN: 0194-911X
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB The genes encoding inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2, also known as prostaglandin-endoperoxide synthase-2) are induced in many types of cells in response to proinflammatory cytokines. The authors have previously shown that interleukin-1β (IL) stimulates iNOS and COX-2 mRNA in cardiac myocytes. Because IL has been shown to activate mitogen-activated protein kinase (MAPK) signaling pathways in many different cells, the authors tested whether the p42/44 and p38 MAPK pathways were involved in IL stimulation of iNOS and COX-2, using a specific inhibitor of p42/44 activation, PD98059 (PD), and the p38 inhibitor SB205380 (SB). Nitrites were measured using the Griess reagent, PGE2 by an enzyme immunoassay, iNOS and COX-2 protein by Western blot anal., and iNOS mRNA by Northern blot anal. Tested sep., the p38 kinase and MAPK inhibitors partially reduced IL stimulation of nitrite, iNOS protein, and iNOS mRNA; used together, they completely abolished the effect of IL. SB and PD inhibited IL-stimulated COX-2 protein by 60% and 80%, resp., and IL-stimulated COX-2 protein was totally prevented by the combination of inhibitors. PGE2 production was inhibited >99% by either drug alone, suggesting a posttranslational effect on enzyme activity. To test whether this posttranslational effect involved the cytosolic phospholipase A2 (cPLA2) isoform, Western blots were probed for cPLA2 protein. Evidently IL stimulated cPLA2 activity and synthesis, which was inhibited by SB but not PD. Thus: (1) IL induction of iNOS synthesis depends on both the p42/44 and p38 signaling pathways, acting primarily at the level of transcriptional regulation; and (2) IL regulation of COX-2 synthesis involves the p42/44 and p38 signaling pathways, with an addnl. level of regulation occurring posttranslationally, perhaps at the level of activation of the cPLA2 isoform, which may be involved in intracellular signaling, as well as regulation of arachidonic acid release for COX-2 activity.

RE.CNT 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 102 OF 105 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:72926 CAPLUS
DN 130:218636
TI Norepinephrine-stimulated MAP kinase activity enhances cytokine-induced NO production by rat cardiac myocytes
AU Kan, Hong; Xie, Zirong; Finkel, Mitchell S.
CS Department of Medicine, West Virginia University School of Medicine,

Robert C. Byrd Health Sciences Center, Morgantown, WV, 26506-9157, USA
SO American Journal of Physiology (1999), 276(1, Pt. 2), H47-H52
CODEN: AJPHAP; ISSN: 0002-9513
PB American Physiological Society
DT Journal
LA English
AB The effect of norepinephrine (NE) on cytokine-stimulated nitric oxide (NO) production by cardiac myocytes has not been previously reported. NE alone caused no significant increase in NO2- levels over vehicle. Addition of NE to interleukin-1β (IL-1β) significantly increased inducible NO synthase (iNOS) mRNA expression, iNOS protein, and NO2- production vs. IL-1β alone. Addition of the α-adrenergic blocker prazosin or the β-adrenergic blocker propranolol partially reduced the NE-mediated increase in iNOS mRNA expression and NO2- production Addition of prazosin and propranolol together completely abolished the NE-induced increase in iNOS mRNA expression and NO2- production NE significantly enhanced mitogen-activated protein (MAP) kinase activity that was reduced by prazosin, propranolol, and PD-98059, a selective MAP kinase kinase inhibitor. Addition of PD-98059 reduced the NE-mediated increase in iNOS mRNA expression and NO2- production The authors report for the first time that NE enhances IL-1β-stimulated NO production by activation of α- and β-adrenergic receptors through a novel MAP kinase mechanism.
RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 103 OF 105 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:645565 CAPLUS
DN 129:340068
TI Regulation of mitogen-activated protein kinase phosphatase-1 induction by insulin in vascular smooth muscle cells, Evaluation of the role of the nitric oxide signaling pathway and potential defects in hypertension
AU Begum, Najma; Ragolia, Louis; Rienzie, Jennifer; McCarthy, Marguerite; Duddy, Noreen
CS Diabetes Research Laboratory, Winthrop University Hospital, Mineola, NY, 11501, USA
SO Journal of Biological Chemistry (1998), 273(39), 25164-25170
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB In this study, the authors examined the regulation of mitogen-activated protein kinase phosphatase (MKP-1) expression by insulin in primary vascular smooth muscle cell cultures. Insulin caused a rapid time- and dose-dependent induction of MKP-1 mRNA and protein expression. Blockade of nitric oxide synthase (NOS) with NG-monomethyl-L-arginine acetate, and cGMP with RpcGMP, completely inhibited MKP-1 expression. Insulin-mediated MKP-1 expression was preceded by inducible NOS (iNOS) induction and cGMP production Blockade of phosphatidylinositol 3-kinase (PI3-kinase) signaling with wortmannin inhibited insulin-mediated iNOS protein induction, cGMP production, and MKP-1 expression. To evaluate potential interactions between NOS and the mitogen-activated protein kinase (MAPK) signaling pathways, the authors employed PD98059 and SB203580, two specific inhibitors of ERKs and p38 MAPK. These inhibitors abolished the effect of insulin on MKP-1 expression. Only PD98059 inhibited insulin-mediated iNOS protein induction. Vascular smooth muscle cells from spontaneous hypertensive rats exhibited a marked decrease in MKP-1 induction due to defects in insulin-induced iNOS expression because of redns. in PI3-kinase activity. Treatment with sodium nitroprusside and 8-bromo-cGMP restored MKP-1 mRNA expression to levels comparable with controls. The authors conclude that insulin-induced MKP-1 expression is mediated by PI3-kinase-initiated signals, leading to the induction of iNOS and elevated cGMP levels that stimulates MKP-1 expression.
RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 104 OF 105 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:397180 CAPLUS
DN 129:148018
TI Role of MAP kinase cascades in inducing arginine transporters and nitric oxide synthetase in RAW264 macrophages
AU Caivano, Matilde
CS Department of Biochemistry, MRC Protein Phosphorylation Unit, University of Dundee, Dundee, DD1 4HN, UK
SO FEBS Letters (1998), 429(3), 249-253
CODEN: FEBLAL; ISSN: 0014-5793
PB Elsevier Science B.V.
DT Journal
LA English
AB Bacterial lipopolysaccharide (LPS) in the presence of interferon gamma (IFNγ) stimulates the synthesis of the cationic amino acid transporter 2B (CAT-2B) and inducible nitric oxide synthetase (iNOS) in RAW264 macrophages, which are thought to underlie the increased rate of arginine uptake into these cells and its conversion to nitric oxide, resp. Here, the authors demonstrates that the LPS- and IFNγ-induced increase in arginine uptake into RAW264 cells is partially suppressed in the presence of PD 98059, partially suppressed in the presence of SB 203580, and completely inhibited by both drugs. In contrast, the LPS- and IFNγ-induced synthesis of CAT-2B mRNA and iNOS protein is unaffected by PD 98059 and SB 203580. The results indicate that the MAPK/ERK and SAPK2/p38 cascades are both rate-limiting for LPS- and IFNγ-stimulated arginine uptake, but not for iNOS synthesis. They also suggest that PD 98059 and SB 203580 suppress CAT-2B synthesis at a post-transcriptional level.
RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 105 OF 105 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1998:129074 CAPLUS
DN 128:256329
TI Extracellular signal-regulated kinase and p38 subgroups of mitogen-activated protein kinases regulate inducible nitric oxide synthase and tumor necrosis factor-α gene expression in endotoxin-stimulated primary glial cultures
AU Bhat, Narayan R.; Zhang, Peisheng; Lee, John C.; Hogan, Edward L.
CS Department of Neurology, Medical University of South Carolina, Charleston, SC, 29425, USA
SO Journal of Neuroscience (1998), 18(5), 1633-1641
CODEN: JNRSDS; ISSN: 0270-6474
PB Society for Neuroscience
DT Journal
LA English
AB Tumor necrosis factor-α (TNFα) and nitric oxide (NO), the product of inducible NO synthase (iNOS), mediate inflammatory and immune responses in the CNS under a variety of neuropathol. situations. They are produced mainly by "activated" astrocytes and microglia, the two immune regulatory cells of the CNS. Here, the authors examined the regulation of TNFα and iNOS gene expression in endotoxin-stimulated primary glial cultures, focusing on the role of mitogen-activated protein (MAP) kinase cascades. The bacterial lipopolysaccharide (LPS) was able to activate extracellular signal-regulated kinase (ERK) and p38 kinase subgroups of MAP kinases in microglia and astrocytes. ERK activation was sensitive to PD98059, the kinase inhibitor that is specific for ERK kinase. The activity of p38 kinase was inhibited by SB203580, a member of the novel class of cytokine suppressive anti-inflammatory drugs (CSAIDs), as revealed by blocked activation of the down-stream kinase, MAP kinase-activated protein kinase-2. The treatment of glial cells with either LPS alone (microglia) or a combination of LPS and interferon-γ (astrocytes) resulted in an induced production of NO and TNFα. The two kinase inhibitors, at micromolar concns., individually suppressed and, in combination, almost completely blocked

glial production of NO and the expression of iNOS and TNFα, as determined by Western blot anal. Reverse transcriptase-PCR anal. showed changes in iNOS mRNA levels that paralleled iNOS protein and NO while indicating a lack of effect of either of the kinase inhibitors on TNFα mRNA expression. The results demonstrate key roles for ERK and p38 MAP kinase cascades in the transcriptional and post-transcriptional regulation of iNOS and TNFα gene expression in endotoxin-activated glial cells.

RE.CNT 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s l4 (L) "MAP"
87554 "MAP"
L9 152 L4 (L) "MAP"

=> d 150-152 bib abs

L9 ANSWER 150 OF 152 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1983:616305 CAPLUS
DN 99:216305
TI The MAP/GLOBUS Campaign 1983
AU Offermann, D.
CS Wuppertal Univ., Fed. Rep. Ger.
SO Eur. Space Agency, [Spec. Publ.] ESA SP (1983), ESA SP-183, ESA Symp. Eur. Rocket Balloon Programmes Relat. Res., 6th, 161-6
CODEN: ESPUD4
DT Report
LA English
AB An international campaign of ground-based, airplane, balloon, and rocket expts. is planned for Sept. 1983 at Aire-sur-l'Adour, France) to monitor, stratospheric O3 and NOx constituents, atmospheric dynamics, and solar irradiation
Scientific objectives, experiment designs, and the sonde/balloon flight schedules of the program are surveyed, briefly.

L9 ANSWER 151 OF 152 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1983:47937 CAPLUS
DN 98:47937
TI Cloning of alkaline phosphatase isozyme gene (iap) of Escherichia coli
AU Nakata, Atsuo; Shinagawa, Hideo; Amemura, Mitsuko
CS Res. Inst. Microb. Dis., Osaka Univ., Suita, 565, Japan
SO Gene (1982), 19(3), 313-19
CODEN: GENED6; ISSN: 0378-1119
DT Journal
LA English
AB In E. coli, 3 major alkaline phosphatase [9001-78-9] isoenzymes are formed by mol. conversions which depend on physiol. conditions. A chromosomal gene, iap, is responsible for alkaline phosphatase isoenzyme conversion and is assumed to code for a proteolytic enzyme that removes the arginine residue(s) from the N-terminal position of alkaline phosphatase subunits. A chromosomal fragment which complemented the Iap- phenotype was cloned into plasmid pBR322 by a shotgun method. The transducing phage λiap was constructed in vitro from the chromosomal fragment containing the iap gene and λtna DNA. The integration site of the phage on the chromosome was identified as the iap locus by phage P1 transduction, which meant that the cloned chromosomal DNA contained an authentic iap gene. A restriction **map** of the hybrid plasmid was constructed. Based upon this information, several iap deletion plasmids as well as smaller iap+ plasmids were constructed. Anal. of the phenotypes conferred by these plasmids located the iap gene within a 2-kilobase (kb) segment of the cloned DNA. The cells carrying the iap+ plasmid showed very efficient isoenzyme conversion even in a medium containing L-arginine [**74-79-3**], an inhibitor for the isoenzyme conversion. This indicates overprodn. of the iap gene product.

L9 ANSWER 152 OF 152 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1979:474100 CAPLUS
DN 91:74100
TI Electron density maps of bent bonds in noncyclic molecules
AU Eisenstein, M.; Hirshfeld, F. L.
CS Dep. Struct. Chem., Weizmann Inst. Sci., Rehovot, Israel
SO Chemical Physics (1979), 38(1), 1-10
CODEN: CMPHC2; ISSN: 0301-0104
DT Journal
LA English
AB Electron-d. maps, derived exptl. (x-ray diffraction) or theor. (extended-basis SCF calcns.), show that bond bending due to unbalanced 1,3-steric repulsions is expressed in a deformation-d. peak slightly displaced off the bond axis. This is demonstrated in (NH2)2C:NCN, HN3, N3CN, HCO2H, and HN:NH. Besides accounting for tilted Me groups, as in MeOH, and numerous similar violations of local symmetry, the flexible-spring model rationalizes a variety of conformational effects, such as the preferred syn-planar conformation of carboxylic acids, where the axis of internal rotation does not coincide with the internuclear vector.

=> s l4 (L) mapk
13262 MAPK
L10 61 L4 (L) MAPK

=> d 60-61 bib abs

L10 ANSWER 60 OF 61 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:768068 CAPLUS
DN 132:76548
TI Transmembrane signaling mechanisms regulating expression of cationic amino acid transporters and inducible nitric oxide synthase in rat vascular smooth muscle cells
AU Baydoun, Anwar R.; Wileman, Samantha M.; Wheeler-Jones, Caroline P. D.; Marber, Michael S.; Mann, Giovanni E.; Pearson, Jeremy D.; Closs, Ellen I.
CS Department of Biosciences, Faculty of Natural Sciences, University of Hertfordshire, Herts, AL10 9AB, UK
SO Biochemical Journal (1999), 344(1), 265-272
CODEN: BIJOAK; ISSN: 0264-6021
PB Portland Press Ltd.
DT Journal
LA English
AB The signaling mechanisms involved in the induction of nitric oxide synthase and L-arginine transport were investigated in bacterial lipopolysaccharide (LPS)- and interferon-γ (IFN-γ)-stimulated rat cultured aortic smooth muscle cells (RASMCs). The expression profile of transcripts for cationic amino acid transporters (CATs) and their regulation by LPS and IFN-γ were also examined Control RASMCs expressed mRNA for CAT-1, CAT-2A and CAT-2B. Levels of all three transcripts were significantly elevated in activated cells. Stimulated CAT mRNA expression and L-arginine transport occurred independently of protein kinase C (PKC), protein tyrosine kinase (PTK) and p44/42 mitogen-activated kinases (MAPKs), but were inhibited by the p38 MAPK inhibitor SB203580, which at 3 μM caused maximum inhibition of both responses. Induction of NO synthesis was independent of p44/42 MAPK activation and only marginally dependent on PKC, but was attenuated markedly by the PTK inhibitors genistein and herbimycin A. SB203580 differentially regulated inducible NO synthase expression and NO production, potentiating both processes at low micromolar concns. and inhibiting at concns. of ≥ 1 μM. In conclusion, our results suggest that RASMCs constitutively express transcripts for CAT-1, CAT-2A and CAT-2B, and that expression of these transcripts is significantly enhanced by LPS and IFN-γ. Moreover, stimulation of L-arginine transport and induction of NO synthesis by LPS and IFN-γ appear to be under critical

regulation by the p38 MAPK, since both processes were significantly modified by SB203580 at concns. so far shown to have no effect on other signaling pathways. Thus, in RASMCs, the p38 MAPK cascade represents an important signaling mechanism, regulating both enhanced L-arginine transport and induced NO synthesis.
RE.CNT 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 61 OF 61 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:142654 CAPLUS
DN 130:309383
TI Hyaluronan in joint cavitation
AU Ward, A. C.; Dowthwaite, G. P.; Pitsillides, A. A.
CS Dep. Veterinary Basic Sciences, The Royal Veterinary Coll., Univ. London, London, NW1 0TU, UK
SO Biochemical Society Transactions (1999), 27(2), 128-135
CODEN: BCSTB5; ISSN: 0300-5127
PB Portland Press Ltd.
DT Journal; General Review
LA English
AB A review with 48 refs., describing several key characteristics of cells at sites of joint cavitation, which suggest that differential increases in hyaluronan synthesis and its interaction with hyaluronan-binding proteins are essential for joint cavitation. Preliminary finding are presented that suggest that specific signalling pathways, including strain-related NO production and MAPK activation, might be involved in the mechano-modulatory influence of movement during joint formation.
RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s l4 (L) HIV
63471 HIV
L11 282 L4 (L) HIV

=> d 280-282 bib abs

L11 ANSWER 280 OF 282 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1991:403519 CAPLUS
DN 115:3519
TI Mapping of HIV-1 Tat protein sequences required for binding to Tar RNA
AU Kamine, James; Loewenstein, Paul; Green, Maurice
CS Sch. Med., St. Louis Univ., St. Louis, MO, 63110, USA
SO Virology (1991), 182(2), 570-7
CODEN: VIRLAX; ISSN: 0042-6822
DT Journal
LA English
AB A gel retardation assay was used to study the binding of chemical synthesized domains of the HIV-1 Tat protein to radiolabeled trans-activating response element (Tar) RNA. As with recombinant Tat protein, synthetic Tat specifically binds to Tar RNA and not to a defective Tar RNA or to anti-sense Tar RNA. The 6 amino acid portion of the basic region containing five arginines is sufficient to confer Tar binding to overlapping Tat protein fragments; Tat fragments that lack the basic region do not bind Tar. In addition, the basic region alone can also binding Tar RNA; however, binding of the basic region is nonspecific since defective Tar RNA is bound as well as wild-type Tar RNA. Binding specificity for wild-type Tar RNA can be conferred by the addition of a min. of 8 random amino acids to either end of the basic region.

L11 ANSWER 281 OF 282 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1991:139105 CAPLUS
DN 114:139105
TI Drug survival in clinical samples irradiated as an anti-HIV precaution
AU De Bree, H.; Van Berkel, M. P.

CS Duphar B. V., Weesp, 1380 DA, Neth.
SO Methodological Surveys in Biochemistry and Analysis (1990), 20(Anal. Drugs Metab., Incl. Anti-Infect. Agents), 221-5
CODEN: MSBADU; ISSN: 0748-6715
DT Journal
LA English
AB A study was conducted to ascertain what γ-irradiation dose was needed to inactivate HIV in clin. samples. The authors also investigated whether radiation affected the levels of drugs and endogenous components in plasma. Doses of ≥5 Mrad inactivated the virus without detriment to most test drugs or, except for blood enzymes, to constituents of interest to clin. chemists.

L11 ANSWER 282 OF 282 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1990:441332 CAPLUS
DN 113:41332
TI Preparation of peptide amides as human immunodeficiency virus inhibitors
IN Handa, Balraj Krishan; Machin, Peter James; Martin, Joseph Armstrong; Redshaw, Sally; Thomas, Gareth John
PA Hoffmann-La Roche, F., und Co. A.-G., Switz.
SO Eur. Pat. Appl., 69 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 346847	A2	19891220	EP 1989-110717	19890613
	EP 346847	A3	19911023		
	EP 346847	B1	19940511		
	R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	CA 1340588	A1	19990608	CA 1989-601434	19890601
	US 5157041	A	19921020	US 1989-362621	19890605
	ZA 8904285	A	19900228	ZA 1989-4285	19890606
	AU 8936130	A1	19891214	AU 1989-36130	19890607
	AU 624144	B2	19920604		
	HU 51254	A2	19900428	HU 1989-2903	19890607
	HU 205898	B	19920728		
	DK 8902863	A	19891214	DK 1989-2863	19890612
	DK 172747	B1	19990628		
	NO 8902407	A	19891214	NO 1989-2407	19890612
	NO 175715	B	19940815		
	NO 175715	C	19941123		
	JP 02042048	A2	19900213	JP 1989-149265	19890612
	JP 2515019	B2	19960710		
	KR 9705905	B1	19970422	KR 1989-8040	19890612
	FI 8902881	A	19891214	FI 1989-2881	19890613
	FI 95693	B	19951130		
	FI 95693	C	19960311		
	AT 105549	E	19940515	AT 1989-110717	19890613
	ES 2052815	T3	19940716	ES 1989-110717	19890613
	US 5446161	A	19950829	US 1992-916812	19920720
	US 5554756	A	19960910	US 1995-391380	19950217
	US 5652369	A	19970729	US 1995-394523	19950406
	US 5620987	A	19970415	US 1995-398478	19950410
PRAI	GB 1988-13940	A	19880613		
	GB 1989-8035	A	19890410		
	US 1989-362621	A3	19890605		
	EP 1989-110717	A	19890613		
	US 1992-916812	A3	19920720		

OS MARPAT 113:41332
AB R1R2NCHR3CONHCHR4CR5R6CH2N(:O)nR7CHR8R9 [I; R1 = alkoxycarbonyl, aralkoxycarbonyl, (ar)alkanoyl, cycloalkylcarbonyl, aroyl, heterocyclylcarbonyl, alkylsulfonyl, etc.; R2 = H; R1R2N = cyclic aromatic imide; R3 = (cyclo)alkyl, (aryl)alkyl, aryl, heterocyclylalkyl,

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                   visualization tools
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 NEWS 10  OCT 27   EPFULL enhanced with additional content
 NEWS 11  NOV 14   CA/CAplus - Expanded coverage of German academic research

 NEWS EXPRESS  NOVEMBER 18 CURRENT VERSION FOR WINDOWS IS V8.01,
               CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 13 JUNE 2005.
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=> s sb203580 or sb202474
          1897 SB203580
            30 SB202474
L1        1902 SB203580 OR SB202474

=> s l1 and hiv
         63471 HIV
L2          12 L1 AND HIV

=> d 1-12 bib abs hitstr
```

L2 ANSWER 1 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2005:174383 CAPLUS
DN 142:278560
TI p38 MAPK-dependent and YY1-mediated chemokine receptors CCR5 and CXCR4 up-regulation in U937 cell line infected by Mycobacterium tuberculosis or Actinobacillus actinomycetemcomitans
AU Lei, JianQiang; Wu, ChunLan; Wang, XiaoLei; Wang, HongHai
CS State Key Laboratory of Genetic Engineering, Institute of Genetics, School of Life Science, Fudan University, Shanghai, 200433, Peop. Rep. China
SO Biochemical and Biophysical Research Communications (2005), 329(2), 610-615
CODEN: BBRCA9; ISSN: 0006-291X
PB Elsevier
DT Journal
LA English
AB We have found previously that the chemokine receptors CCR5 and CXCR4, which are the coreceptors of **HIV**, are up-regulated in human macrophage cell line U937 infected by Mycobacterium tuberculosis (MTB). This suggests another possibility to explain the co-infection of MTB and **HIV**. In order to detect the up-regulation of CCR5 and CXCR4 as a unique phenomenon of MTB infection or a ubiquitous phenomenon of pathogenic bacteria, we investigated the expression changes of these two chemokine receptors in macrophages attacked by another bacterium Actinobacillus actinomycetemcomitans (AA) (from mRNA level and protein level). To reveal the mol. mechanism of these expression changes, p38 MAPK special inhibitor **SB203580** was used and the expression of CCR5 and CXCR4 neg. regulator YY1 transfactor was analyzed. Finally, we

conclude that the up-regulation of CCR5 and CXCR4 can at least partially contribute to the down-regulation of transfactor YY1 which is p38 MAPK pathway-dependent and this up-regulation has little relationship with MTB and **HIV** co-infection.

RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 2 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2005:9235 CAPLUS
DN 142:86675
TI Vanilloid receptor 1 inhibitors for treatment of human immunodeficiency virus (**HIV**)-mediated neuropathies and pain states
IN Bouchon, Axel; Misawa, Keiko
PA Bayer Healthcare AG, Germany
SO Eur. Pat. Appl., 42 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI EP 1493438	A1	20050105	EP 2003-15052	20030703
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
WO 2005002551	A2	20050113	WO 2004-EP6679	20040621
WO 2005002551	A3	20051006		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
PRAI EP 2003-15052	A	20030703		

AB The invention relates to the application of Vanilloid receptor (VR) 1 inhibitors for drug development and for the treatment of **HIV** -mediated neuropathies and neuropathic pain states. Further, the inventor identified a novel signaling cascade connecting the **HIV** receptor CXCR4 to VR1. Thus, the invention provides mol. evidence that **HIV** -mediated pain states - initiated upon binding of the virus to CXCR4 - can be inhibited by VR1 antagonists blocking the final execution of the CXCR4NR1 pathway. In addition, the invention demonstrates that present standard therapies for **HIV**-mediated pain (which do not include VR1 inhibitors) can not interfere with the CXCR4/VR1 pathway thus explaining inefficient patient treatment in the clinics. N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)-N'-(4-trifluoromethoxy-benzyl)urea (preparation given) completely inhibited gp120-mediated calcitonin gene-related peptide release from dorsal root ganglion neurons.

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:1155870 CAPLUS
DN 142:106809
TI The **HIV** protease inhibitor ritonavir synergizes with butyrate for induction of apoptotic cell death and mediates expression of heme oxygenase-1 in DLD-1 colon carcinoma cells
AU Muehl, Heiko; Paulukat, Jens; Hoefler, Sonja; Hellmuth, Markus; Franzen, Rochus; Pfeilschifter, Josef
CS Pharmazentrum Frankfurt, University Hospital, Johann Wolfgang

Goethe-Universitaet Frankfurt am Main, Frankfurt am Main, D-60590, Germany
SO British Journal of Pharmacology (2004), 143(7), 890-898
CODEN: BJPCBM; ISSN: 0007-1188
PB Nature Publishing Group
DT Journal
LA English
AB The protease inhibitor ritonavir is an integral part of current antiretroviral therapy targeting human immunodeficiency virus. Recent studies demonstrate that ritonavir induces apoptotic cell death with high efficiency in lymphoblastoid cell lines. Moreover, ritonavir can suppress activation of the transcription factor nuclear factor-κB and is an inhibitor of interleukin-1β and tumor necrosis factor-α production in peripheral blood mononuclear cells. Thus, ritonavir appears to have anti-inflammatory properties. In the present study, the authors investigated in DLD-1 colon carcinoma cell effects of ritonavir on apoptotic cell death and expression of heme oxygenase-1 (HO-1), an anti-inflammatory enzyme that may be critically involved in the modulation of colonic inflammation. Compared to unstimulated control, ritonavir resulted in a moderate increase in the rate of apoptotic cell death as observed after 20 h of incubation. Notably, ritonavir potently synergized with the short-chain fatty acid butyrate for induction of caspase-3-dependent apoptosis in DLD-1 cells. Ritonavir enhanced mRNA and protein expression of HO-1 in DLD-1 cells. Ritonavir-induced HO-1 protein was suppressed by **SB203580** or SB202190 and preceded by immediate upregulation of cellular c-Fos and c-Jun protein levels. This process was associated with induction of activator protein-1 as detected by electrophoretic mobility shift anal. The present data suggest that ritonavir has the potential to curb colon carcinogenesis by reducing cell growth via mechanisms that include apoptosis and by simultaneously modulating colonic inflammation via induction of anti-inflammatory HO-1.
RE.CNT 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:985685 CAPLUS
DN 142:16432
TI Inhibition of Melanoma Growth and Metastasis by ATF2-Derived Peptides
AU Bhoumik, Anindita; Gangi, Lisa; Ronai, Ze'ev
CS Department of Oncological Sciences, Mount Sinai School of Medicine, New York, NY, 10029, USA
SO Cancer Research (2004), 64(22), 8222-8230
CODEN: CNREA8; ISSN: 0008-5472
PB American Association for Cancer Research
DT Journal
LA English
AB The resistance of melanoma to apoptosis, as well as its growth and metastasis capabilities, can be overcome by expression of a peptide derived from amino acid (aa) 51 to 100 of ATF2. Here we show that expression of ATF2(51-100) in human melanoma cells reduced their growth in nude mice, which was addnl. inhibited upon treatment with protein kinase inhibitors UCN-01 or **SB203580.** Injection of a fusion protein consisting of HIV-TAT and aa 51 to 100 of ATF2 into SW1 melanomas efficiently inhibits their growth and their metastasis up to complete regression. Addnl., expression of a 10aa peptide that corresponds to aa 51 to 60 of ATF2 sensitizes melanoma cells to spontaneous apoptosis, which coincides with activation of caspase 9 and poly(ADP-ribose) polymerase cleavage, and inhibit their growth in vivo. The 10aa peptide increases the association of c-Jun NH2-terminal kinase with c-Jun but not with ATF2, resulting in concomitant increase in TRE-mediated transcription. Our study points to mechanisms underlying the activities of the ATF2 peptide while highlighting its possible use in drug design.
RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 5 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN

AN 2004:441294 CAPLUS
DN 142:272
TI Suppression of **HIV**-1 viral replication and cellular pathogenesis by a novel p38/JNK kinase inhibitor
AU Muthumani, Karuppiah; Wadsworth, Scott A.; Dayes, Nathanael S.; Hwang, Daniel S.; Choo, Andrew Y.; Abeysinghe, Harindra R.; Siekierka, John J.; Weiner, David B.
CS Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA, USA
SO AIDS (London, United Kingdom) (2004), 18(5), 739-748
CODEN: AIDSET; ISSN: 0269-9370
PB Lippincott Williams & Wilkins
DT Journal
LA English
AB Objective: To analyze a novel compound, which inhibits serine-threonine protein kinase p38, for its possible bioactivity against **HIV**-1 infection. Methods: Proteins involved in cellular signal transduction pathways represent a novel class of host therapeutic targets for infectious diseases. In this regard the serine/threonine kinase p38 MAPK, a member of the mitogen-activated protein (MAP) kinase superfamily of signal transduction mols. may play an important role in **HIV**-1 infection. We analyzed the ability of this compound (RWJ67657) to inhibit **HIV** replication in primary T-cells and monocytes. Cellular expression of phospho-p38MAPK was studied by Western blot anal. Blockade of **HIV** infection induced apoptosis was measured by Annexin V staining. Results: p38 inhibitor RWJ67657 was effective in inhibiting **HIV**-1 replication in both T-cell and monocyte cell lines, irresp. of the coreceptor used by the virus for entry into the cell. Importantly, both reverse transcriptase and protease resistant escape mutant viruses were effectively suppressed by RWJ67657. In addition, the tested compds. block **HIV**-induced T-cell apoptosis, a critical means of T-cell depletion linked to AIDS progression. Conclusion: Several steps in the **HIV**-1 virus life cycle appear to depend on cellular activation, including activation of the p38 pathway. Without activation virus replication is thought to be blocked due to incomplete reverse transcription and a lack of proviral DNA integration. The data collectively illustrate that inhibition of the p38 pathway can affect **HIV**-1 replication. Interruption of **HIV** infection by p38 inhibitors underscores the value of exploring antiviral drugs that target host cellular proteins.
RE.CNT 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:368885 CAPLUS
DN 140:386047
TI Cytomodulating peptides and methods for treating neurological disorders
IN Iyer, Suhasini; Buelow, Roland; Lazarov, Mirella; Fong, Timothy
PA Sangstat Medical Corporation, USA
SO PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 3

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004037196	A2	20040506	WO 2003-US33602	20031024

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,

FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004186052 A1 20040923 US 2003-693331 20031024

WO 2005009457 A1 20050203 WO 2004-US15506 20040517

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2002-421297P P 20021024

US 2002-431420P P 20021205

US 2003-470839P P 20030515

AB Compns. and methods are provided for inhibiting neuronal cell death and the loss of neuronal contacts resulting from acute and chronic neurol. disorders, including neurodegenerative and neuroinflammatory diseases. The compns. and methods utilize RDP-58 compns. capable of providing a direct neuroprotective effect on neuronal cells in conjunction with inhibition of autoimmune and inflammatory processes.

L2 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN

AN 2003:991282 CAPLUS

DN 140:35936

TI A method for using tethered bis(polyhydroxyphenyls) and O-alkyl derivatives thereof in treating inflammatory conditions of the central nervous system

IN Hensley, Kenneth L.; Floyd, Robert A.

PA Oklahoma Medical Research Foundation, USA

SO PCT Int. Appl., 94 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003103583	A2	20031218	WO 2003-US17621	20030605
WO 2003103583	A3	20040624		
WO 2003103583	C1	20040722		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2488609	AA	20031218	CA 2003-2488609	20030605
US 2004014721	A1	20040122	US 2003-455235	20030605
EP 1549301	A2	20050706	EP 2003-736838	20030605

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, SK

JP 2005533042	T2	20051104	JP 2004-510704	20030605

PRAI US 2002-387374P P 20020610

WO 2003-US17621 W 20030605

OS MARPAT 140:35936

AB The present invention involves the use tethered bis(polyhydroxyphenyl) compds. to slow the progression of neurol. diseases in which pro-inflammatory cytokine stimulation of microglial cells is reasonably

anticipated to make a significant contribution to disease pathol. Diseases for which this is the case include amyotrophic lateral sclerosis (AlS) and other motor neuron diseases (MNDs) of similar clin. presentation; Parkinson's disease (PD); Alzheimer's disease (AD); spino-bulbar atrophy; (SBA); Huntington's disease (HD); myasthenia gravis (MG); multiple sclerosis (MS); **HIV**-associated dementia; fronto-temporal dementia (FTD); stroke; encephalomyelitis; traumatic brain injury; age-related retinal degeneration; and other neurol. diseases possessing microglial activation as a contributing pathol. feature. Specific examples are presented where the tethered bis(polyhydroxyphenyl) compound is resveratrol; piceatannol; nordihydroguaiaretic acid (NDGA), curcumin, or sesamin.

L2 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:749635 CAPLUS
DN 139:374861
TI Morphine Negatively Regulates Interferon-γ Promoter Activity in Activated Murine T Cells through Two Distinct Cyclic AMP-dependent Pathways
AU Wang, Jinghua; Barke, Roderick A.; Charboneau, Richard; Loh, Horace H.; Roy, Sabita
CS Dep. Pharmacol., Univ. Minnesota, Minneapolis, MN, 55455, USA
SO Journal of Biological Chemistry (2003), 278(39), 37622-37631
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB To explore the mechanism by which morphine promotes the incidence of **HIV** infection, the authors evaluated the regulatory role of morphine on the interferon-γ (IFN-γ) promoter in activated T cells from wild type and μ-opioid receptor knockout mice. The results show that morphine inhibited anti-CD3/CD28-stimulated IFN-γ promoter activity in a dose-dependent manner. Chronic morphine treatment of T cells increased intracellular cAMP. To evaluate the role of cAMP in morphine's modulatory function, the effects of dibutyryl cAMP and forskolin were investigated. Both dibutyryl cAMP and forskolin treatment inhibited IFN-γ promoter activity. Treatment with pertussis toxin, but not with a protein kinase A inhibitor, antagonized morphine's inhibitory effects. Morphine inhibited phosphorylation of ERK1/2 and p38 MAPK; in addition, morphine treatment in the presence of either ERK1/2 or p38 MAPK inhibitor (PD98059 or **SB203580**) resulted in an additive inhibition of IFN-γ promoter activity. The transcription factor activator protein-1, NF-κB, and nuclear factor of activated T cells (NFAT) were neg. regulated by morphine. Overexpression of NF-κB p65 rescued the inhibitory effect of morphine on IFN-γ promoter activity. However, only when NFATc1 was co-overexpressed with c-fos was the inhibitory effect of morphine on IFN-γ promoter counteracted. The inhibitory effects of morphine were not observed in T cells obtained from μ-opioid receptor knockout mice, suggesting that morphine modulation of IFN-γ promoter activity is mediated through the μ-opioid receptor. In summary, the data indicate that morphine modulation of IFN-γ promoter activity is mediated through two distinct cAMP-dependent pathways, the NF-κB signaling pathway and the ERK1/2, p38 MAPK, AP-1/NFAT pathway.
RE.CNT 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 9 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:728599 CAPLUS
DN 137:277656
TI Vpr- and Nef-Dependent Induction of RANTES/CCL5 in Microglial Cells
AU Si, Qiusheng; Kim, Mee-Ohk; Zhao, Meng-Liang; Landau, Nathaniel R.; Goldstein, Harris; Lee, Sunhee C.
CS Department of Pathology, Albert Einstein College of Medicine, Bronx, NY, 10461, USA

SO Virology (2002), 301(2), 342-353
CODEN: VIRLAX; ISSN: 0042-6822
PB Elsevier Science
DT Journal
LA English
AB Microglia are pivotal in the pathogenesis of AIDS dementia, as they serve as the major target of **HIV** infection in the CNS. In addition, activation of microglia correlates best with clin. dementia. Although the β-chemokine RANTES/CCL5 is important in modulating **HIV** infection as well as cellular activation, no information is available regarding how its expression is regulated in microglia by **HIV**-1. Here the authors report that RANTES/CCL5 expression is induced in microglia by **HIV**-1, but that this requires infection by **HIV**-1. This conclusion was supported by (1) the delayed kinetics coinciding with viral replication; (2) the lack of effect of X4 viruses; (3) inhibition by the reverse transcriptase inhibitor AZT, and (4) the lack of effect of cytokine antagonists or antibodies. Interestingly, RANTES/CCL5 production was dependent on the viral accessory protein Vpr, in addition to Nef, demonstrating a novel role for Vpr in chemokine induction in primary macrophage-type cells. Furthermore, the specific p38 MAP kinase inhibitor **SB203580** augmented chemokine expression in microglia, indicating a neg. role played by p38. These data suggest unique features of RANTES/CCL5 regulation by **HIV**-1 in human microglial cells.
RE.CNT 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 10 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:278972 CAPLUS
DN 133:28079
TI Role of the p38 and MEK-1/2/p42/44 MAP kinase pathways in the differential activation of human immunodeficiency virus gene expression by ultraviolet and ionizing radiation
AU Taher, Mohiuddin M.; Hershey, Chad M.; Oakley, Jacqueline D.; Valerie, Kristoffer
CS Department of Radiation Oncology, Massey Cancer Center, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA, 23298-0058, USA
SO Photochemistry and Photobiology (2000), 71(4), 455-459
CODEN: PHCBAP; ISSN: 0031-8655
PB American Society for Photobiology
DT Journal
LA English
AB UV radiation is a potent activator of human immunodeficiency virus (**HIV**) gene expression in a HeLa cell clone having stably integrated copies of an HIVcat (cat gene under control of the **HIV** promoter) reporter construct, whereas ionizing radiation is ineffective. UV-activated **HIV** gene expression is completely blocked by the specific p38 mitogen-activated protein (MAP) kinase inhibitor **SB203580** and by expression of a kinase-inactive p38 mutant that interferes with normal p38 function, suggesting that this stress-activated protein kinase plays an important role in UV-mediated transcriptional activation of **HIV**. In support of these findings, we show here that Western blot anal. demonstrated rapid and significant activation of p38 MAP kinase by UV. On the other hand, γ-radiation activated p38 MAP kinase very poorly in HeLa cells at both low and high doses at times (5-30 min) when UV radiation was effective. UV radiation also activated **HIV** gene expression (≤9-fold) in 1G5 Jurkat T-cells stably transfected with a luciferase reporter gene under control of the **HIV** promoter. In these cells, γ-radiation stimulated **HIV** gene expression but to a lesser extent (≤3-fold) and with different kinetics than after UV radiation, and this response was obliterated by the incubation of cells with the mitogen-activated protein kinase/Erk kinase (MEK)-1/2 inhibitor PD98059. This result suggests that in these cells signaling in response to γ-radiation is transduced through the MEK-1/2/p42/44 MAP kinase pathway to increase **HIV** gene expression. All combined, these results suggest that activation of

p38 MAP kinase is necessary for efficient **HIV** gene expression triggered by DNA damaging agents, and, in a cell type-specific manner, activation of the MEK-1/2/p42/44 MAP kinase pathway is important for triggering a response to γ-radiation. Thus, it appears as if UV signaling leading to **HIV** gene expression requires the p38 MAP kinase pathway whereas activation by γ-radiation requires the MEK-1/2/p42/44 MAP kinase pathway.

RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 11 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:580102 CAPLUS
DN 131:297126
TI Genetic Evidence That Stress-Activated p38 MAP Kinase Is Necessary but Not Sufficient for UV Activation of **HIV** Gene Expression
AU Taher, Mohiuddin M.; Baumgardner, Timothy; Dent, Paul; Valerie, Kristoffer
CS Department of Radiation Oncology and Massey Cancer Center Medical College of Virginia, Virginia Commonwealth University, Richmond, VA, 23298-0058, USA
SO Biochemistry (1999), 38(40), 13055-13062
CODEN: BICHAW; ISSN: 0006-2960
PB American Chemical Society
DT Journal
LA English
AB We have examined the role of stress-activated p38 MAP kinase in regulating human immunodeficiency virus (**HIV**) gene expression in response to UV light (UV). We found that UV activated p38 in HeLa cells harboring stably integrated copies of an HIVcat plasmid to levels similar to those obtained by hyperosmotic shock. However, hyperosmotic shock resulted in one order of magnitude smaller increase in CAT activity than treatment with UV. The specific p38 inhibitor **SB203580** significantly decreased (>80%) UV activation of **HIV** gene expression whereas PD98059, a specific MEK-1 inhibitor did not, suggesting that p38 is specifically involved in the **HIV** UV response and little to no contribution is provided by MEK-1 and the p42/p44 MAP kinase pathway. Whereas increased binding of NF-κB to an oligonucleotide spanning the **HIV** enhancer was observed after UV, as expected, this binding was not affected by **SB203580**. Furthermore, UV activation of **HIV** gene expression in cells having the cat reporter gene under control of an **HIV** promoter deleted of the enhancer (-69/+80) produced results indistinguishable from those using HIVcat/HeLa cells with an intact **HIV** promoter (-485/+80), suggesting that **SB203580** acts through the basal transcription machinery. Northern blot anal. of steady-state RNA from HIVcat/HeLa cells revealed an almost complete inhibition of UV activation with **SB203580** at the RNA level. Similarly, the UV response was almost completely obliterated at the CAT and RNA levels in HIVcat/HeLa cells stably transfected with a plasmid expressing a kinase-inactive mutant of p38 (isoform α), without affecting NF-κB activation, providing strong genetic evidence that p38, at least the α isoform, is necessary for UV activation of **HIV** gene expression and that NF-κB activation alone is insufficient. These results firmly establish p38 MAP kinase as a key modulator of **HIV** gene expression in response to UV that acts independently of NF-κB.

RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L2 ANSWER 12 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
AN 1996:732804 CAPLUS
DN 126:30209
TI Activation of the **HIV**-1 long terminal repeat by cytokines and environmental stress requires an active CSBP/p38 MAP kinase
AU Kumar, Sanjay; Orsini, Michael J.; Lee, John C.; McDonnell, Peter C.; Debouck, Christine; Young, Peter R.
CS Dep. Mol. Immunol., SmithKline Beecham Pharmaceuticals, King of Prussia,

PA, 19406, USA
SO Journal of Biological Chemistry (1996), 271(48), 30864-30869
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB The human immunodeficiency virus, type 1 (**HIV**-1) promoter is known to be activated by proinflammatory cytokines and UV light. These stimuli also activate various members of the mitogen-activated protein kinase family, including JNK/SAPK and CSBP/p38. In HeLa cells containing an integrated **HIV**-1 long terminal repeat (LTR)-driven reporter, we now show that the specific p38 inhibitor, **SB203580**, inhibits activation of the **HIV**-1 LTR by interleukin-1, tumor necrosis factor, UV light, and osmotic stress. Inhibition was 70-90% in all but the case of tumor necrosis factor stimulation, where inhibition was 50%. Each of these stimuli activated p38, which was inhibited by **SB203580** in vitro and in vivo with an IC50 (between 0.1 and 1 μM) similar to that required to inhibit transcription. In contrast, **SB203580** had no effect on JNK, which was also activated by these stimuli. The NFκB sites in the **HIV**-1 LTR were required for a response to cytokines but not to UV, and **SB203580** remained capable of inhibiting UV activation in the absence of the NFκB sites. Studies in which **SB203580** was added at different times relative to UV stimulation suggested that the critical p38-mediated phosphorylation event occurred between 2 and 4 h after UV treatment. These data indicate that p38 is required for **HIV**-1 LTR activation but that the action of p38 is delayed, presumably due to substrate unavailability or inaccessibility.

=> file reg

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FULL ESTIMATED COST	39.27	39.48
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CA SUBSCRIBER PRICE	-8.76	-8.76

FILE 'REGISTRY' ENTERED AT 18:28:26 ON 25 NOV 2005

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 24 NOV 2005 HIGHEST RN 868731-40-2
DICTIONARY FILE UPDATES: 24 NOV 2005 HIGHEST RN 868731-40-2

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* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
*
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Structure search iteration limits have been increased. See HELP SLIMITS for details.

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http://www.cas.org/ONLINE/UG/regprops.html

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=> s l2
             0 SB203580
             0 SB202474
           771 HIV
L3           0 L1 AND HIV

=> file medline
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                               14.23      53.71

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)    SINCE FILE      TOTAL
                                                   ENTRY    SESSION
CA SUBSCRIBER PRICE                                0.00      -8.76

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 FILE LAST UPDATED: 25 NOV 2005 (20051125/UP). FILE COVERS 1950 TO DATE.

 On December 19, 2004, the 2005 MeSH terms were loaded.

 The MEDLINE reload for 2005 is now available. For details enter HELP
 RLOAD at an arrow promt (=>). See also:

    http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

 OLDMEDLINE now back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2005 vocabulary.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s l3 and hiv
             0 L3
        153349 HIV
L4           0 L3 AND HIV

=>

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COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
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FULL ESTIMATED COST                                    0.38       54.09

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)        SINCE FILE      TOTAL
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 NEWS  3  SEP 09  ACD predicted properties enhanced in REGISTRY/ZREGISTRY
 NEWS  4  OCT 03  MATHDI removed from STN
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                 to core patent offices
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               http://download.cas.org/express/v8.0-Discover/

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